Petitioner's Demonstratives

Gene Company Pty Ltd. v. The Trustees of Colombia University in the City of New York

IPR2024-00313

U.S. Patent No. RE47045

GENE COMPANY - EXHIBIT1088
Gene Company PTY LTD, v.The Trustees of Columbia University in the City of New York
IPR2024-00313

WILSON SONSINI

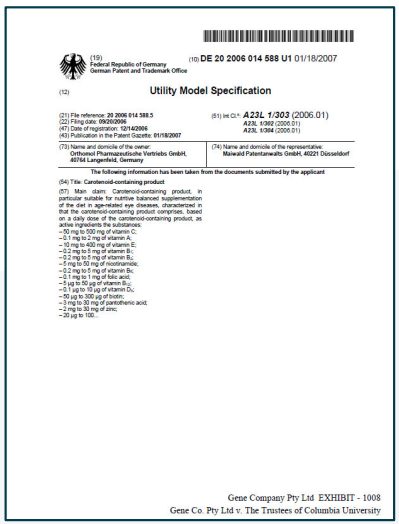
*** Objections Not Subject to MTE Omitted from Deposition Quotes Throughout***

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

March 27, 2025

Instituted Grounds

Claims	Challenge
1-9, 19-23, 25-26, 28-36, 46-50, 52-53	**Ground 1:** Obvious over Ortho Pharma and Olson 1988
10-15, 18, 37-42, 45	**Ground 2:** Obvious over Ground 1 in further view of Mata
16-17, 24, 27, 43-44, 51, 54	**Ground 3:** Obvious over Ground 1 and 2 in further view of Widder



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(74) Name and domicile of the representative: Maiwald Patentanwalts GmbH, 40221 Düsseldorf

The following information has been taken from the documents submitted by the applicant

(54) Title: Carotenoid-containing product

(57) Main claim: Carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, characterized in that the carotenoid-containing product 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;
– 0.2 mg to 5 mg 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...

Gene Company Pty Ltd EXHIBIT - 1008
Gene Co. Pty Ltd v. The Trustees of Columbia University



Journal of Labelled Compounds and Radiopharmaceuticals Vol. XIV, No. 1

SYNTHESIS OF TRI-, TETRA-, AND PENTA-DEUTERATED FORMS OF VITAMIN A

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SUMMARY

The synthesis of 20,20,20-trideutero, 19,20,20,20-tetradeutero, 12,19,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate, by a modified Wittig-Horner reaction, is described. The key step is a base-catalyzed epimerization of appropriate intermediates. The 10,19,19,19-$^2H_4$-vitamin A, because of its high isotopic integrity (>95% $^2H_4$), is the preferred analog for biological studies of vitamin A metabolism.

Keywords: Deuterated vitamin A analogues, deuterated retinyl acetate, 20,20,20-$^2H_3$-retinyl acetate, 19,20,20,20-$^2H_4$-retinyl acetate, 12,19,20,20,20-$^2H_5$-retinyl acetate, 10,19,19,19-$^2H_4$-retinyl acetate, retinoic synthesis.

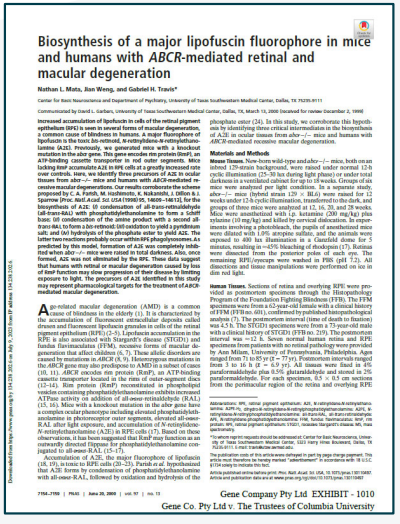
INTRODUCTION

For studying the metabolism of vitamin A in humans, nonradioactive deuterated or ^{13}C labeled compounds of high purity are desired (1). Because the natural abundance of ^{13}C in retinol, a C-20 compound, is 22% at M+1 and 4.5% at M+2, deuterated compounds should contain three or more deuteriums in metabolically and chemically stable positions to provide adequate analytical sensitivity.

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Gene Company Pty Ltd EXHIBIT - 1006
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Biosynthesis of a major lipofuscin fluorophore in mice and humans with *ABCR*-mediated retinal and macular degeneration

Nathan L. Mata, Jian Weng, and Gabriel H. Travis*

Communicated by David L. Garbers, University of Texas Southwestern Medical Center, Dallas, TX, March 13, 2000 (received for review December 2, 1999)

Increased accumulation of lipofuscin in cells of the retinal pigment epithelium (RPE) is seen in several forms of macular degeneration, a common cause of blindness in humans. A major fluorophore of lipofuscin is the toxic bis-retinoid, N-retinylidene-N-retinylethanolamine (A2E). Previously, we generated mice with a knockout mutation in the *abcr* gene. This gene encodes rim protein (RmP), an ATP-binding cassette transporter in rod outer segments. Mice lacking RmP accumulate A2E in RPE cells at a greatly increased rate over controls. Here, we identify three precursors of A2E in ocular tissues from *abcr*−/− mice and humans with *ABCR*-mediated recessive macular degenerations. Our results corroborate the scheme proposed by C. A. Rotzer, J. Lichtenthaler, K. Nakanishi, and T. Ogura (Japanese Patent Kokai No. Sho 64-79900 [P], 6/8/89–14/3/2), for the biosynthesis of A2E. Condensation of ocular all-*trans*-retinal (all-*trans*-RAL) with phosphatidylethanolamine to form a Schiff base, till condensation of the amine product with a second all-*trans*-RAL to form a bis-retinoid, (ii) oxidation to yield a pyridinium salt, and (iv) hydrolysis of the phosphate ester to yield A2E. The latter two reactions probably occur within RPE phagolysosomes. As predicted by this model, formation of A2E was completely inhibited when *abcr*−/− mice were raised in total darkness. Also, once formed, A2E was not eliminated by the RPE. These data suggest that humans with retinal or macular degeneration caused by loss of RmP 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.

Age-related macular degeneration (AMD) is a common cause of blindness in the elderly (1). It is characterized by the accumulation of fluorescent extracellular deposits called drusen and fluorescent lipofuscin granules in cells of the retinal pigment epithelium (RPE) (2). Accumulation of lipofuscin in RPE is also associated with Stargardt's disease (STGD1) and fundus flavimaculatus (FFM), recessive forms of macular degeneration that affect children (3, 7). These allelic disorders are caused by mutations in *ABCR* (8, 9), filamentgrous mutations in the *ABCR* gene may also predispose to AMD in a subset of cases (10, 11). *ABCR* encodes rim protein (RmP), an ATP-binding cassette transporter located in the rims of outer-segment discs (12–14). Rim protein (RmP) reconstituted in phospholipid vesicles containing phosphatidylethanolamine exhibits increased ATPase activity on addition of all-*trans*-retinaldehyde (RAL) (15, 16). Mice with a knockout mutation in the *abcr* gene have a complex ocular phenotype including elevated phosphatidylethanolamine in photoreceptor outer segments, elevated all-*trans*-RAL after light exposure, and accumulation of N-retinylidene-N-retinylethanolamine (A2E) in RPE cells (17). Based on these observations, it has been suggested that RmP may function as an outward translocator of phosphatidylethanolamine conjugated to all-*trans*-RAL (15–17).

Accumulation of A2E, the major fluorophore of lipofuscin (18, 19), is toxic to RPE cells (20–23). Parish *et al.* hypothesized that A2E forms by condensation of phosphatidylethanolamine with all-*trans*-RAL, followed by oxidation and hydrolysis of the phosphate ester (24). In this study, we corroborate this hypothesis by identifying three critical intermediates in the biosynthesis of A2E in ocular tissues from *abcr*−/− mice and humans with *ABCR*-mediated recessive macular degeneration.

Materials and Methods

Mouse Tissues. Nine-born wild-type and *abcr*−/− mice, both on an inbred 129-strain background, were raised under normal 12-h cyclic illumination (25–30 lux during light phase) or under total darkness in a ventilated cabinet for up to 10 weeks. Groups of all mice were analyzed per light condition. In a separate study, *abcr*−/− mice (hybrid strain 129 × BL6) were raised for 12 weeks under 12-h cyclic illumination, transferred to the dark, and groups of mice euthanized after 1, 11, 15, 21, 28, and 28 weeks. Mice were first anesthetized with ketamine (200 mg/kg) plus xylazine (40 mg/kg) and killed by cervical dislocation. In experiments involving a photobleach, the pupils of anesthetized mice were dilated with 1.0% atropine sulfate, and the animals were exposed to 400 lux illumination in a Claridisk dome for 5 minutes, resulting in ≈45% bleaching of rhodopsin (17). Retinas were dissected from the posterior poles of each eye. The remaining RPE/eyecups were washed in PBS (pH 7.2). All dissections and tissue manipulations were performed on ice in dim red light.

Human Tissues. Sections of retina and overlying RPE were provided as postmortem specimens through the Histopathology Program of the Foundation Fighting Blindness (FFB). The FFM specimens were from a 62-year-old female with a clinical history of FFM (FFB no. 691), confirmed by published histopathological findings (25). The postmortem interval was 4 h. The STGD1 specimen was 1.5 h. The STGD1 specimen was from a 35-year-old male with a clinical history of STGD1 (FFB no. 219). The postmortem interval was ≈12 h. Seven normal human retina and RPE specimens from patients with no retinal pathology were provided by Ann Milam, University of Pennsylvania, Philadelphia. Ages ranged from 71 to 85 yr (± = 77 yr). Postmortem intervals ranged from 3 to 10 h (± = 6.9 yr). All tissues were fixed in 4% paraformaldehyde plus 0.5% glutaraldehyde and stored in 2% paraformaldehyde. For each specimen, 0.5 × 0.5 cm sections from the peripacular region of the retina and overlying RPE

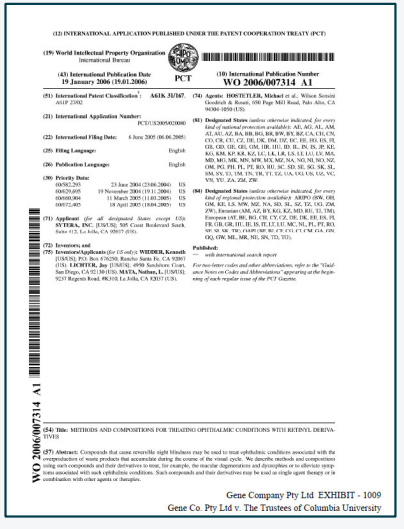
Abbreviations: RPE, retinal pigment epithelium; A2E, N-retinylidene-N-retinylethanolamine; A2PE, N-retinylidene-N-retinylphosphatidylethanolamine; A2PL, N-retinylidene-N-retinylphosphatidylethanolamine; all-*trans*-RAL, all-*trans*-retinaldehyde; APL, N-retinylidene-phosphatidylethanolamine; FFM, fundus flavimaculatus; RmP, rim protein; RPE, retinal pigment epithelium; STGD1, recessive Stargardt's disease; MA, mass spectrometry.

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Gene Company Pty Ltd EXHIBIT - 1010
Gene Co. Pty Ltd v. The Trustees of Columbia University



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WO 2006/007314 A1

(54) Title: METHODS AND COMPOSITIONS FOR TREATING OPHTHALMIC CONDITIONS WITH RETINYL DERIVATIVES

(57) Abstract: Compounds that cause reversible sight 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 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.

Gene Company Pty Ltd EXHIBIT - 1009
Gene Co. Pty Ltd v. The Trustees of Columbia University

Pet. 1-2, 21-23, 46-48, 55-56; Paper 13, 2, 51-52.

Representative Claims

1. A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid, wherein the C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal, and C_{20}-D_{1-3}-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier.

28. A method of treating a macular degeneration, comprising administering an effective amount of a substituted C_{20}-D_{1-3}-retinoid to a patient in need thereof, wherein the substituted C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal and C_{20}-D_{1-3}-pro-vitamin A carotenoids.

29. A method of treating a macular degeneration, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid, wherein the C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal and C_{20}-D_{1-3}-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier.

Claims Encompass:

- C_{20}-D_{1-3} Vitamin A / ß-carotene
- In any pharmaceutically-acceptable carrier (claims 1 & 29) or not (28).
  - **nutraceutical** composition (claims 3 and 31).
- Patient broadly in need of treating a macular degeneration, including:
  - AMD (claims 5 & 32)
  - Dry AMD (claims 10 & 37)
  - Stargardt (claims 11 & 38)
  - Sorsby's fundus dystrophy (claims 16 & 43)
  - Retinitis Pigmentosa (claims 16 & 43)

Pet., iv-viii, 1-2, 21-24, 32, 43, 46-48, 53, 55-56; Paper 13, 2, 51-52; EX1002, ¶191; EX1004, ¶¶37, 175.

Narrowest Compound:
C20-D3 Retinol Acetate

What is claimed is:

1. A method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C_{20}-D_{1-3}-retinoid, wherein the C_{20}-D_{1-3}-retinoid is selected from the group consisting of C_{20}-D_{1-3}-retinol, C_{20}-D_{1-3}-retinol ester, C_{20}-D_{1-3}-retinal, and C_{20}-D_{1-3}-pro-vitamin A carotenoids, and a pharmaceutically acceptable carrier.

2. The method according to claim **1**, wherein the substituted C_{20}-D_{1-3}-retinoid is a C_{20}-D_3-retinoid.

6. The method according to claim **5**, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_{1-3}-retinol or a C_{20}-D_{1-3}-retinol ester.

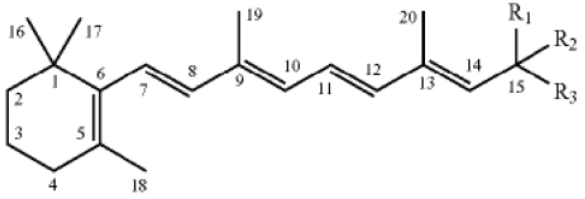
7. The method according to claim **5**, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol, a C_{20}-D_3-retinol ester, C_{20}-D_3-retinal, or a C_{20}-D_3-pro-vitamin A carotenoid.

8. The method according to claim **5**, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

14. The method according to claim **11**, wherein the C_{20}-D_{1-3}-retinoid is C_{20}-D_3-retinol acetate.

EX1001, Claims.

(Ib)



wherein

R_1 and R_2 are both H and R_3 is OH (retinol); or

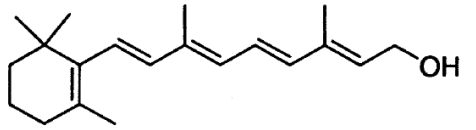
R_1 and R_2 are both H and R_3 is $OCOCH_3$ (retinol acetate); or

R_1 and R_2 are both H and R_3 is OCOR (retinol ester such as, e.g., retinol palmitate) or

R_1 is =O, R_2 is nothing and R_3 is OH (retinoic acid) or

R_1 is H, R_3 is nothing, and R_2 is =CH—R_7, where R_7 forms a carotenoid. In this embodiment, R_7 together with the rest of the compound forms, e.g., a beta-carotene or another pro-vitamin A carotenoid such as the deuterated beta-carotene shown in formulae Ib' below:

EX1001, 10:35-12:65.



all-*trans*-retinol

EX1050.

Pet., 34, 50-51; Pet. Reply, 18-19, 23-25; EX1002, ¶¶59-60.

Independent claims are obvious

Grounds Reference	Patient in need of treatment for macular degeneration / reducing lipofuscin formation	C_{20}-D_3-retinol acetate	Pharmaceutically acceptable carrier
Ortho Pharma	✓		✓
Olson 1988		✓	

Straightforward combination:

- Ortho Pharma discloses treating macular degeneration patients (in need of reducing lipofuscin formation) with an **effective amount of vitamin A/ß-carotene** in pharmaceutically-acceptable carrier. *E.g.*, EX1008, ¶¶ [0001], [0007]-[0008], [0051].
- Olson 1988 discloses making and purifying claimed **C_{20}-D_3-retinol** and **C_{20}-D_3-retinol acetate**. *E.g.*, EX1006, Abstract, 12-13, 15-19.

Pet., 21-23, 23-27, 28-29, 30-31; EX1008, ¶[0008]; EX1006, Abstract, 12-13, 15-19.

Dependent claims are obvious

Claim Limitation	Ortho Pharma	Olson 1988
Claims 2, 7-8, 30, 34-35: C_{20}-D_3-retinoid or carotenoid		✓
Claims 3 and 31: Nutraceutical	✓	
Claim 4: Macular degeneration patient	✓	
Claims 5 and 32: AMD patient	✓	
Claims 6-8, 33-35: Retinol, retinol ester, retinol acetate		✓
Claims 9, 26, 36, and 53: Reduced A2E formation		✓
Claims 19 and 46: Dosage 0.1-90 mg/day	✓	
Claims 20-23, 47-50: Additional actives	✓	
Claims 25 and 52: Additional active carotenoids	✓	

Pet., 31-39.

Ground 2: Dependent Claims 10-15, 18, 37-42, 45

Ground 1 + Mata (EX1010)

- Identifies additional claimed retinal diseases treated with vitamin A or associated with undesirable A2E/lipofuscin formation

Claim Limitation	Ortho Pharma	Olson 1988	Mata
Claims 10 and 37: Dry AMD patient	✓		✓
Claims 11 and 38: Stargardt patient			✓
Claims 12-14, 39-41: Retinol, ester, acetate		✓	
Claims 13-14, 40-41: C_{20}-D_3-retinoid/carotenoid		✓	
Claims 15 and 42: Reduced A2E formation		✓	
Claims 18 and 45: ABCA4-linked MD patient			✓

Pet., 46-55.

Ground 3: Dependent Claims 16-17, 24, 27, 43-44, 51, 54

Grounds 1 and 2 + Widder (EX1009)

- Identifies significant downsides of interfering with visual cycle.
- Describes co-administering A2E/lipofuscin prophylactic PLUS phospholipids to ameliorate existing A2E/lipofuscin.
- Discloses direct application to eye.

Claim Limitation	Ortho Pharma	Olson 1988	Mata	Widder
Claims 16 and 43: MD is SFD, RP, etc.				✓
Claims 17 and 44: C_{20}-D_3-retinol acetate		✓		
Claims 24 and 51: Phospholipid add'l active				✓
Claims 27 and 54: Administer directly to eye				✓

Pet., 55-65.

Ortho Pharma (EX1008)

Method of treating a macular degeneration

[0052] 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.

15. Use of a carotenoid-containing product according to any one of the preceding claims for the manufacture of an agent for the dietary treatment of eye diseases, in particular age-related eye diseases such as age-related macular degeneration or senile cataract.

EX1008.

[0001] 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.

[0002] It 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.

[0011] 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.

[0025] Providing the eye with carotenoids may particularly help to provide nutritive support for the eye in age-related macular degeneration or senile cataracts.

[0054] 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.

Pet., 21-23, 23-24, 27-28, 30-31; EX2192, ¶152; POR, 17.

Ortho Pharma (EX1008)

Administering effective amount of vitamin A / ß-carotene

19. The method according to claim **1**, wherein the substituted C_{20}-D_{1-3}-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.

46. The method according to claim 29, wherein the substituted C_{20}-D_{1-3}-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.

EX1001, Claims 19, 48.

[0008] This task is solved by 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;

* * *

– 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;

EX1008.

[0019] In preferred embodiments of the carotenoid-containing product according to the invention, the carotenoid-containing product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances:

– 100 mg to 350 mg, preferably 160 mg to 310 mg of vitamin C;

– 0.3 mg to 1.5 mg, preferably 0.4 mg to 1.1 mg of vitamin A;

* * *

– secondary plant compounds selected from the group comprising

14 mg to 22 mg, preferably 15 mg to 20 mg of carotenoids comprising carotenoids selected from the group consisting of beta-carotene, lutein, zeaxanthin, and lycopene, and

[0036] In further preferred embodiments, the carotenoid-containing product comprises, 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:

– 200 mg to 2300 mg, preferably 440 mg to 1600 mg, preferred 700 mg to 1400 mg of vitamin C;

– 0.4 mg to 9 mg, preferably 1.3 mg to 6.7 mg, preferred 1.7 mg to 5 mg of vitamin A;

* * *

25 mg to 150 mg, preferably 60 mg to 100 mg, preferred 65 mg to 90 mg of carotenoids, thereof preferably

* * *

2 mg to 25 mg, preferably 4.4 mg to 13.5 mg, preferred 6.5 mg to 11.5 mg of beta-carotene, and

Pet., 21-23, 23-26, 27-28, 30-31.

Ortho Pharma (EX1008)

Administering effective amount of vitamin A / ß-carotene

Trial Confirmed: Ortho Pharma's vitamin A / ß-carotene correspond to prior art effective amounts.

Q. So that range of 6 to 32 milligrams of carotenoids, kind of in the middle of that is the 15-milligram dose of beta-carotene that was used in the AREDS study; right?

A. So 15 milligrams of beta-carotene would fall within those borders, yes.

EX1069 (Del Priore Depo. Tr.), 119:2-7.

Q. So here on the very first page, just in this, sort of the first list of ingredients that shows up in the patent, it gives a dosage of 0.1 milligrams to 2 milligrams of vitamin A; is that correct?

A. Yes, that is correct.

Q. And that basically sort of encompasses a range right around the middle of which is the RDA for vitamin A; is that fair?

A. The recommended daily allowance is in the middle of that range, yes.

EX1069 (Del Priore Depo. Tr.), 116:21-117:6.

Q. So if we are talking about the vitamin A and the beta-carotene used in the AREDS study by patients who were taking the treatment combination and Centrum vitamin, that is consistent with what the Ortho Pharma reference is saying in paragraph 8, where it says you can have .1 to 2 milligrams vitamin A and also you can have 6 milligrams to 32 milligrams of carotenoids including beta-carotene; correct?

* * *

A. So it's consistent with the dosage that is described in the Ortho Pharma patent document.

EX1069 (Del Priore Depo. Tr.), 119:8-20.

A. Daily requirements of vitamin A are about 900 micrograms in males and about 700 or 750 micrograms in females.

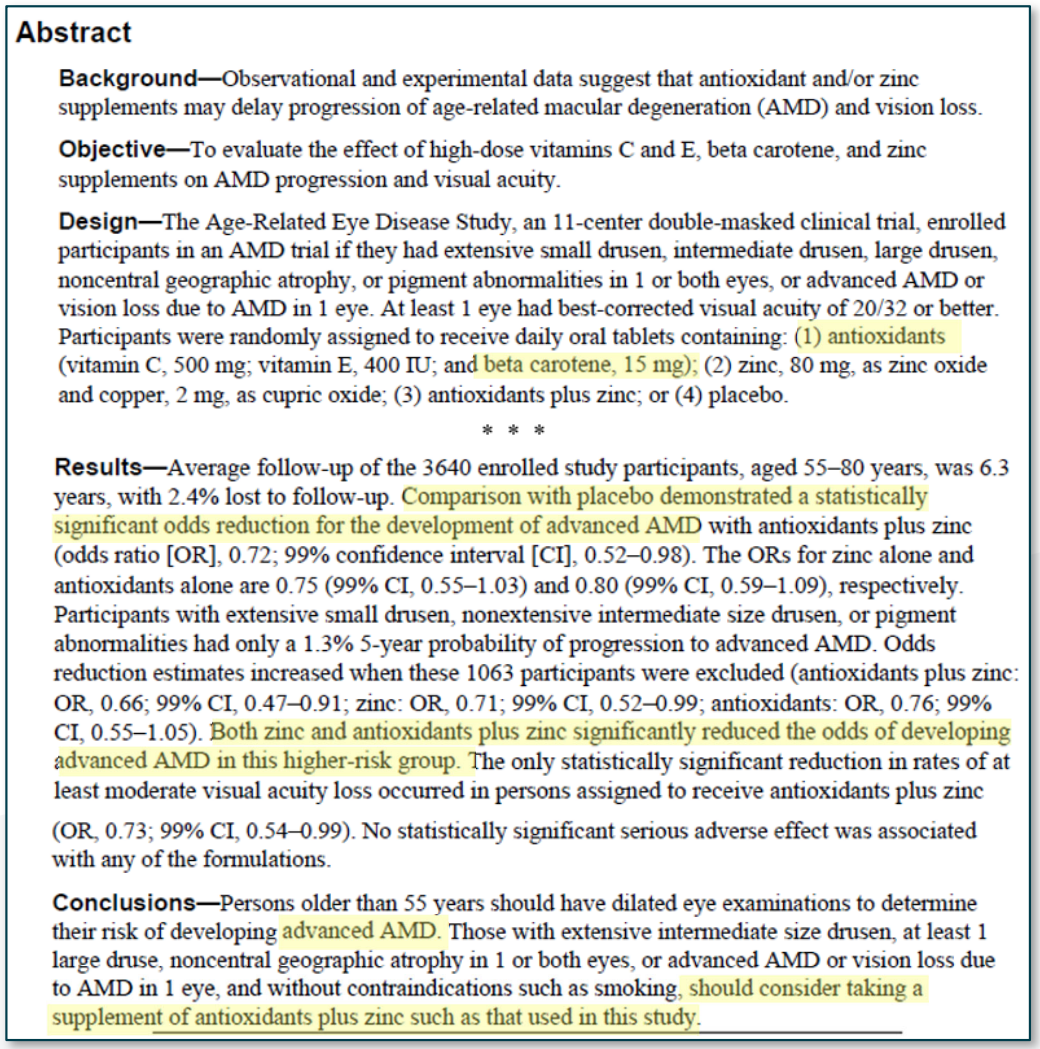
EX1069 (Del Priore Depo. Tr.), 60:4-6.

Pet., 9-10, 21-23, 23-26, 28, 30-31, 43; Pet. Reply, 2-5.

Technological Background

AREDS (EX1022)

Phase 3 study demonstrated **efficacy for AMD** by administering effective amount of vitamin A/ß-carotene.



Abstract

Background—Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

Objective—To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity.

Design—The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

* * *

Results—Average follow-up of the 3640 enrolled study participants, aged 55–80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52–0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55–1.03) and 0.80 (99% CI, 0.59–1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47–0.91; zinc: OR, 0.71; 99% CI, 0.52–0.99; antioxidants: OR, 0.76; 99% CI, 0.55–1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54–0.99). No statistically significant serious adverse effect was associated with any of the formulations.

Conclusions—Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.

EX1022 (AREDS), Abstract.

Q. You referred to beta-carotene as a provitamin. Is beta-carotene a provitamin A carotenoid?

A. Beta-carotene is a provitamin for vitamin A, and the word "carotenoid" corresponds to that chemical class, and it is definitely a carotenoid.

Q. So it is correct to refer to beta-carotene as a provitamin A carotenoid; correct?

A. It is correct to refer to it as a provitamin for vitamin A, and it's also correct to call it carotenoid.

EX1069 (Del Priore Depo. Tr.), 62:1-12.

Pet., 9-10, 21-23, 23-26, 28, 30-31, 43, 49-50; EX1004, ¶¶82-84; Pet. Reply, 2-3, 15-16.

Technological Background

AREDS (EX1022)

Common by 2007 to treat AMD by administering effective amount of vitamin A/ß-carotene.

84. 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, together with Vitamins C and E, and minerals including zinc and copper (except in tobacco smokers, in whom beta-carotene had been shown to increase the risk of lung cancer).

EX1004 (Calman Decl.), ¶84.

83. 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

EX1004 (Calman Decl.), ¶83.

167. Widder further discloses administering vitamin A with fenretinide to reduce lipofuscin formation to thereby treat macular degeneration. For example, in Example 15 entitled "Combination Therapy Involving Fenretinide, Vitamins and Minerals," Widder provides that:

> Administration of fenretinide in combination with vitamins and minerals can be either orally or parenterally administered at amounts effective to inhibit the development or reoccurrence of macular degeneration. Test dosages are initially in the range of about 20 mg/kg per day of fenretinide with 100-1000 mg vitamin C, 100-600 mg vitamin E, 10,000-40,000 IU vitamin A, 50-200 mg zinc and 1-5 mg copper for 15 to 20 weeks.

EX1009 (Widder), 47:21-27.

EX1002 (Guengerich Decl.), ¶167.

Pet., 9-10, 17, 43; Pet. Reply, 2-3.

Technological Background

AREDS (EX1022)

Trial Confirmed: Common by 2007 to treat AMD by administering effective amount of vitamin A/ß-carotene.

Q. You even testified, haven't you, that based on this AREDS study, which was published in 2001, based on that, it became common to recommend the AREDS combination treatment for those high-risk AMD patients; correct?

A. When the AREDS -- there were pre-publications, so for example, there were lectures at scientific meetings that predated this a little bit. But at around this time, patients coming in with high-risk macular degeneration that had already lost vision in one eye, this was used. This was used.

EX1069 (Del Priore Depo. Tr.), 87:10-21.

Q. Did you ever -- did any of your patients ever use it?

A. Did I ever give any of my patients the AREDS supplement?

Q. Yes.

A. Yes.

Q. And that was common to do; correct?

* * *

A. I would give my patients the AREDS supplement, yes. Recommend them.

EX1069 (Del Priore Depo. Tr.), 87:22-88:6.

was seen in patients with early or intermediate AMD. *Id.* at 12. Thus, it was common to recommend AREDS supplements (i.e., the combination of zinc plus antioxidants, including beta-carotene) for high-risk individuals who had experienced bleeding in one eye but not for patients with earlier disease. However, the AREDS study

EX2192 (Del Priore Decl.), ¶96.

Pet., 9-10, 17, 43; Pet. Reply, 2-3.

Technological Background

AREDS (EX1022)

Dr. Del Priore: No Serious AEs, 30% MD risk reduction, "widely distributed" study

Q. I want to talk about serious adverse events. What does the AREDS study tell us about whether there were serious adverse events reported in the study?

* * *

A. So on the top of page 2 of that same paper that we're referring to, the sentence reads -- this is part of their abstract by the way -- no statistically significant serious adverse events were associated with any of the formulations.

EX1069 (Del Priore Depo. Tr.), 88:23-89:17.

A. I would give my patients the AREDS supplement, yes. Recommend them.

Q. What was the risk reduction, the decrease in progression risk for this high-risk population of AMD patients shown in the AREDS study?

A. The reduction of risk in the second eye was about a 30 percent reduction risk.

Q. And was that considered to be meaningful risk reduction at the time?

A. Well, it was better than the alternatives we had, I'll say that much.

Q. You agree that the results of this AREDS study were widely distributed; correct?

* * *

A. "Widely distributed," you mean published and talks at meetings, that sort of thing? Yes. That was done.

EX1069 (Del Priore Depo. Tr.), 88:5-22.

Pet., 9-10, 17, 43; Pet. Reply, 2-3.

Technological Background

AREDS (EX1022)

Majority of AREDS participants also took Centrum multivitamin.

Q. Do you know whether the participants in the AREDS study were permitted to take a multivitamin comprising vitamin A?

A. I'd like to go back and review the entry criteria for the study.

All right. So as part of their enrollment criteria, the second paragraph, which is on the top of page 3 states the percentage of patients who were taking Centrum and their study. At baseline 8 percent were smokers and 67 percent chose to take Centrum. "Of those who elected to take Centrum, 30 percent had been taking multivitamins or a supplement containing a study ingredient for more than five years before study entry."

EX1069 (Del Priore Depo Tr.), 68:8-22.

Q. So you agree that two-thirds of the participants in the AREDS study were taking the Centrum multivitamin supplement; correct?

* * *

A. I'm referring to the same document, page 3, and it basically states that two-thirds or 67 percent chose to take Centrum.

EX1069 (Del Priore Depo. Tr.), 69:7-14; *id.*, 68:23-69:6.

Q. What percentage of your patients would you say take a multivitamin?

A. Between 30 and 50 percent maybe.

Q. Do you discourage your patients from taking a multivitamin?

A. No, I do not.

EX1069 (Del Priore Depo. Tr.), 57:16-21.

Pet. Reply, 2; EX1080, ¶¶75-77, EX1022, 3.

Technological Background

AREDS (EX1022)

Centrum multivitamin provides RDA of vitamin A.

> no statistically significant differences in change from baseline by treatment assignment. The effect of Centrum, which contains RDA doses of the study medications, on serum levels of antioxidants and zinc in this population was negligible.

EX1022, 8





EX1065 (Centrum).

Pet. Reply, 2; EX1080, ¶¶75-77.

Technological Background

AREDS (EX1022)

Trial Confirmed: No genuine dispute Centrum multivitamin provides RDA of vitamin A.

Q. Do you dispute that the Centrum they took had vitamin A?

A. I'm not trying to be difficult, but this just says they were taking Centrum, but I know with Centrum, there is Centrum Silver, there is Centrum Adults, you know, they are vitamins. So I'm just not 100 percent certain that the Centrum formulation they are referring to in here contains vitamin A. It probably does. And I don't know if they are contained in exactly the same dose. I just don't know if it's the same medication or not.

EX1069 (Del Priore Depo. Tr.), 69:23-70:10.

Pet., 9-10, 17, 43; Pet. Reply, 2-5; PO Sur-Reply, 12.

Technological Background

Safe doses

Large doses of vitamin A safely administered **for years**.

Q. Okay. So what they say here is, "We observed no toxic side effects of vitamin A supplementation of 15,000 international units per day for four to six years in our study patients who had an average intake of vitamin A by diet of about 3,600 international units per day." It refers to a table. Correct?

A. That is what they say, yes.

Q. So they are telling us there that these patients had, on average, 18,600 international units of vitamin A every day for four to six years and they observed no toxic side effects; is that correct?

A. That's correct for the average intake. But because it's coming from the diet, you don't know what the doses are in the individual patients, but that is correct from the averages.

Q. And just to be clear, the dose from the supplement was kept constant, but people, their daily intake from diet might vary somewhat; is that correct?

A. Yes.

EX1069 (Del Priore Depo. Tr.), 126:1-22.

Q. That sentence goes on to say, "Vitamin A toxicity from provitamin A sources is largely impossible."

Do you see that?

A. I do see that sentence.

EX1069 (Del Priore Depo. Tr.), 144:18-22.

Q. And under the Conclusions, do you see it says that vitamin A doses of 15 and 22.5 milligrams per day for one year proved safe and equally more efficacious than the 7.5 milligram per day dose and can be recommended for future skin cancer chemo preventative studies?

A. I do see that, yes.

Q. Under the Introduction, the first paragraph, the last sentence of the paragraph says, "Having previously shown that vitamin A doses as high as 300,000 international units per day were well tolerated for up to one year in patients with advanced cancers."

Do you see that?

A. I see that sentence, yes.

Q. That 300,000 international units per day corresponds to approximately 90 milligrams of vitamin A per day; correct?

* * *

A. Yes.

EX1069 (Del Priore Depo. Tr.), 160:10-161:4.

Pet., 9-10, 17, 43; Pet. Reply, 2-5.

Technological Background

Effective doses

Retinitis Pigmentosa (~4 mg); Sorsby's Fundus Dystrophy (~14 mg)

Q. Then the very last sentence of the paragraph, you see where it stays, "Based on these findings and the analysis of decline of ERG amplitude as a function of total vitamin A intake, it is recommended that most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A, 15,000 international units per day, under the supervision of an ophthalmologist," and it goes on to talk about vitamin A.

A. Yes, I do see that.

EX1069 (Del Priore Depo. Tr.), 129:12-22 (Retinitis Pigmentosa).

Q. So in Jacobson, there is -- roughly 12 times your dietary intake of vitamin A is additionally being given to these Sorsby fundus patients; is that correct?

* * *

A. The Sorsby fundus dystrophy patients are receiving much more vitamin A. It would be 50,000 divided by about 3,600.

Q. So I have to add it's almost 14 times?

A. 14.

EX1069 (Del Priore Depo. Tr.), 131:10-20 (Sorsby Fundus).

Q. So earlier we talked about vitamin A had been administered prior to September 2007 to retinitis patients and Stargardt patients.

Are you now comfortable adding Sorsby fundus to the list?

A. This study was before 2007. Yes, I am.

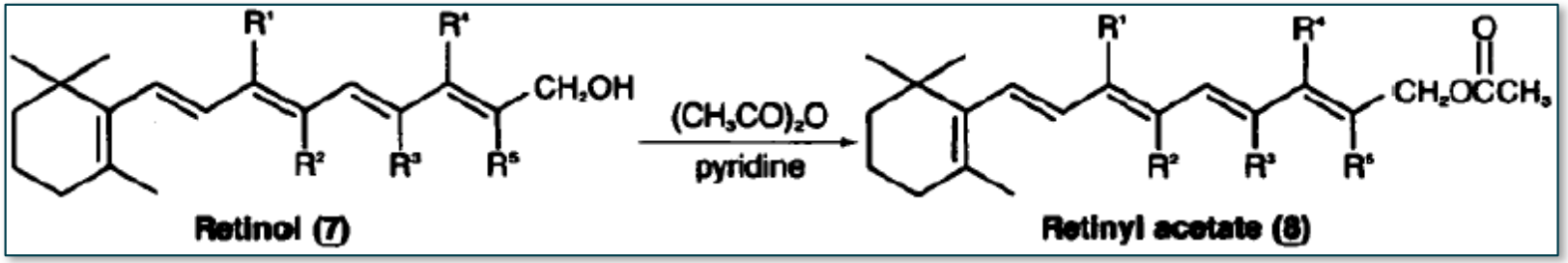
EX1069 (Del Priore Depo. Tr.), 136:11-16 (Sorsby Fundus).

Pet., 9-10, 17, 43; Pet. Reply, 2-5.

Olson 1988 (EX1006)

C_{20}-deuterated vitamin A

Olson 1988 discloses making and purifying claimed C_{20}-D_3-retinol and C_{20}-D_3 retinol acetate.



EX1006, Scheme 2.

20,20,20-$^2H_3$-Retinol 7 (1 g, 0.003 mol) was dissolved in 10 ml pyridine and cooled in an ice bath. Acetic anhydride (0.28 ml, 0.003 mol) was added dropwise. After being stirred 15 min, the solution was allowed to warm to room temperature and checked by TLC; if acetylation was not complete, the solution was cooled, and more acetic anhydride was added. Ice was then added to destroy residual acetic anhydride. The solution was poured into 250 ml hexane and washed with water (6 x 250 ml) to remove pyridine. The organic layer was dried ($MgSO_4$) and rotory-evaporated to give an overall crude yield of 60% (40% cis, 60% all-trans) 20,20,20-$^2H_3$-retinyl acetate 8. The isomers were separated by HPLC (hexane:ethyl acetate, 98:2).

EX1006, 18.

Q. So you agree that the product of the reaction in this paragraph that started with C20 trideuterated retinol compound 7 was C20 trideuterated retinyl acetate compound 8; correct?

A. Yes, it does say that.

* * *

Q. So you agree that the C20 trideuterated retinol acetate in the Olson 1988 reference is the same compound that's claimed by the '045 patent, correct?

* * *

A. They appear to be referring to the same compound, yes.

EX1069 (Del Priore Depo. Tr.), 284:23-285:20.

Pet., 21-23, 23-26, 28, 30-31; Pet. Reply, 18.

Olson 1988 (EX1006)

C_{20}-deuterated vitamin A

Patent Owner wrongly touted this prior art compound as its "novel" invention.

The Examiner maintained the restriction requirement. She noted Applicant's argument that the shared technical feature between the method claims and the pharmaceutical composition claims is the pharmaceutical composition comprising a C_{20} deuterated retinoid. The Examiner rejected this argument because she believes that WO95/04018 (Boehm) discloses such a composition. However, for reasons discussed in the section of this Paper that respond to the obviousness rejection, although WO95/04018 (Boehm) discloses deuterated retinoids, Boehm does not disclose retinoids ***substituted with deuterium at the C_{20} position.*** Moreover, as also discussed in the section of this Paper responding to the obviousness rejection, a pharmaceutical composition comprising a C_{20} deuterium enriched retinoid and a pharmaceutically acceptable carrier or diluent is novel and non-obvious, not only in view of WO95/04018, but also in view of the combination of WO95/04018, Radu, Lang and Widder.

EX1031, 172-173.

Pet., 5, 65-68.

Olson 1988 (EX1006)

C_{20}-deuterated vitamin A

Already in the prior art

Q. You agree that if anyone is calling C20 trideuterated retinol acetate a novel compound, they are mistaken?

* * *

A. I agree that that molecule with three deuteriums is referenced in the 1987 paper.

EX1069 (Del Priore Depo. Tr.), 287:15-22.

Q. And you agree that as of -- before September 2007, the Olson 1988 reference, Exhibit 1006, had already disclosed in the prior art the C20 trideuterated retinol acetate that's claimed in the '045 patent; correct?

* * *

A. I agree that the 1987 paper discloses that molecule.

Q. You agree that in 2007, in September 2007 that that molecule was not a novel molecule; correct?

* * *

A. I agree that that molecule was disclosed in the 1987 publication that we are referring to.

EX1069 (Del Priore Depo. Tr.), 286:2-17.

Pet. Reply, 18.

Ortho Pharma (EX1008)

In a pharmaceutically-acceptable carrier

[0012] A major advantage of the carotenoid-containing product is realized by the use according to the invention of at least two separately present dosage forms, wherein a first dosage form is present in solid form, and a second dosage form is present in liquid form. It 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.

[0037] The carotenoid-containing product may be in the form of at least two separately present dosage forms selected from the group comprising tablets, capsules, powders, granules, solutions and/or effervescent tablets having different compositions of active ingredients. Preferably, the carotenoid-containing product may be in the form of at least three separately present preparation forms, more preferably in the form of at least four separately present preparation forms having the same or different compositions of active ingredients.

[0038] The term "solution" as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein, preferably solids or liquids. Preferred solutions are those that form a mixture of a solvent and substances dissolved therein, in particular active ingredients. A particularly preferred solvent is water.

[0055] Examples of carotenoid-containing products are given below:
It is understood that the dosage forms selected from the group comprising tablets, capsules, powder, granules, solutions, and/or effervescent tablets have the usual excipients used to formulate the respective dosage forms, so that only the active ingredients contained may be listed in the examples.

Pet., 1-4, 16, 21, 27-29; Paper 13 (ID), 29&n.16.

Ortho Pharma (EX1008)

In a pharmaceutically-acceptable carrier

[0050] In preferred embodiments, the carotenoid-containing product may comprise at least one additive, preferably several additives, for improving bioavailability, improving texture, improving solubility and/or improving dissolution rate, disintegrants, shelf-life improving substances, taste-masking substances, taste-improving substances, substances for increasing or decreasing the viscosity, stabilizers, colorants, fillers, mold release agents, and/or disintegration accelerators.

[0051] 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.

[0038] The term "solution" as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein, preferably solids or liquids. Preferred solutions are those that form a mixture of a solvent and substances dissolved therein, in particular active ingredients. A particularly preferred solvent is water.

EX1008.

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, aque-

* * *

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, 15:46-16:6.

[16] In the Petition's section on claim construction, Petitioner does note that "[t]he specification of the '045 patent confirms that the claim term 'pharmaceutically acceptable carrier' encompasses a wide variety of conventional carriers, including water, saline solution, corn oil, and starch." Pet. 21. Patent Owner did not controvert this statement; neither does the

Paper 13 (ID), 29&n.16.

Pet., 1-4, 16, 21, 27-29; Paper 13 (ID), 29&n.16.

Reason to Combine with Reasonable Expectation

progression). A POSA would have had a good reason to employ C_{20}-D_{1-3}-vitamin A (retinol and retinol acetate) in a pharmaceutical composition, such as disclosed in Ortho Pharma, in place of the non-deuterated forms of vitamin A, to retard the accumulation of a lipofuscin pigment in a retina, as motivated by Mata, or to treat a macular degeneration, as disclosed in Ortho Pharma. EX1002, ¶¶257-58.

58, Fig. 5 & Caption. Mata discloses that this synthetic pathway depends on removing a hydrogen atom from C_{20} through a 1,5-sigmatropic shift. EX1010, 7158, Fig. 5. Mata expressly suggests inhibiting this synthetic pathway to reduce lipofuscin formation as a means for treating or preventing macular degeneration. EX1010, 7154 & Abstract, 7159. As Dr. Guengerich explains, a POSA would have been well aware that the 1,5-sigmatropic shift disclosed in Mata was likely a rate-limiting step in A2E-formation and that inhibiting that step in the pathway would reduce A2E formation. EX1002, ¶261.

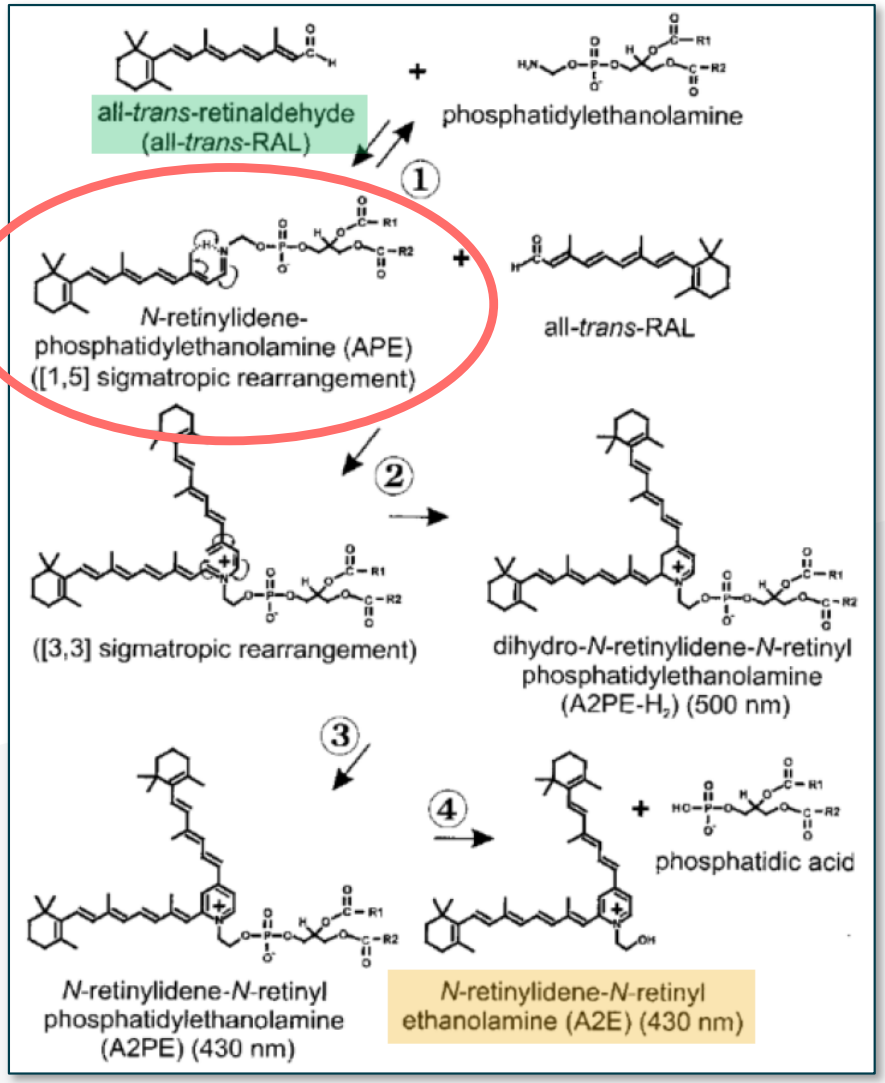
Pet., 40-43.

Reason to Combine with Reasonable Expectation

Mata (EX1010)

- A2E/lipofuscin
  - = unnecessary, undesirable byproduct
  - associated with macular degeneration
  - C_{20}-Hydrogen removal = prerequisite
- C_{20}-deuterated vitamin A likely to slow A2E/lipofuscin formation due to well-known deuterium kinetic isotope effect.
- Obvious to employ C_{20}-deuterated vitamin A in place of effective amount of non-deuterated vitamin A being administered to patients for treatment of lipofuscin-associated ocular diseases, including macular degeneration

E.g., EX1002, ¶¶190-205, 206-217, 218-222, 257-270; EX1004, ¶¶134-149, 150-165, 166-172.



EX1010 (Mata), Fig. 5.

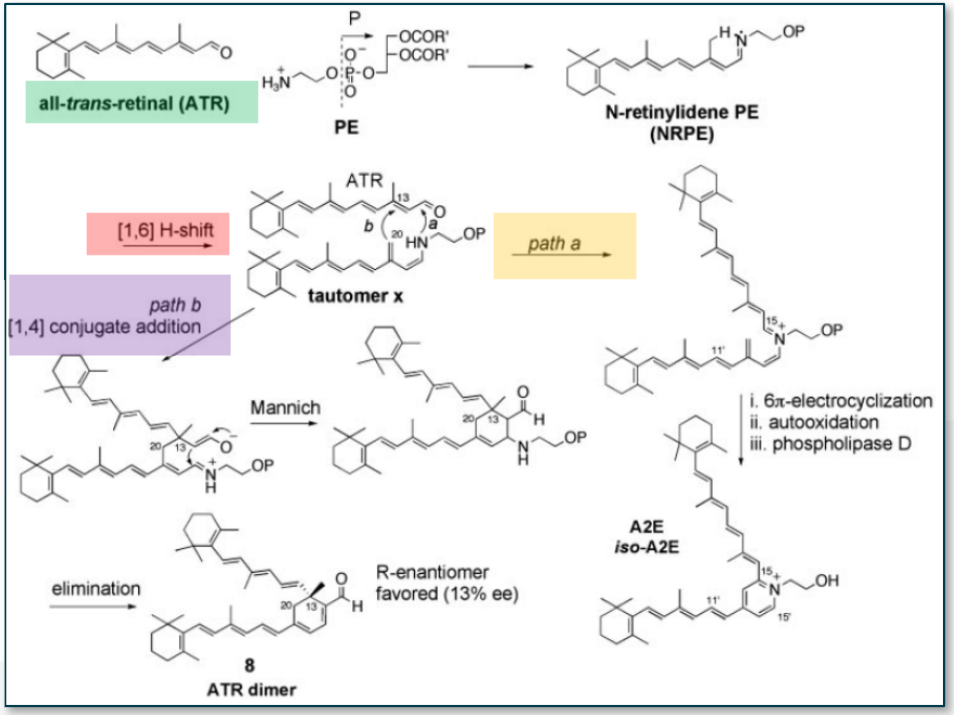
Pet., 1-2, 12, 17-19, 30-31, 36-37, 40-46.

Reason to Combine with Reasonable Expectation

Key Location

- Just upstream of two different lipofuscin pathways
  - A2E
  - ATR-Dimer
- Downstream of visual cycle avoids unnecessary interference with vision

EX1011 (Fishkin), 7095. A person of ordinary skill in the art would have recognized that inhibiting the [1,6] H-shift in Figure 10 of Fishkin was a desirable location for inhibiting the biogenesis of the undesirable lipofuscin because it is upstream of the pathway branch (so will slow both A2E formation and ATR-dimer formation) but is downstream of ATR formation so that it will not interfere with the visual cycle.



EX1011 (Fishkin), Fig. 10.

184. A person of ordinary skill in the art would thus have had good reason to inhibit the [1,5]-sigmatropic shift that was disclosed in Mata to reduce lipofuscin formation associated with ophthalmic disorders including macular degeneration. The [1,5]-sigmatropic shift step in the pathway in the '045 patent is just upstream of the intermediate that results in both A2E and ATR-dimer but sufficiently downstream of ATR formation, thus reducing the formation of undesirable lipofuscin without interfering with the visual cycle. Further, a person of ordinary

EX1002 (Guengerich Decl.), ¶¶85, 184.

Pet., 4, 10-12, 36, 40-43; EX1002, ¶¶84-85, 93; EX1011.

Reason to Combine with Reasonable Expectation

Vitamin A is "essential" for vision

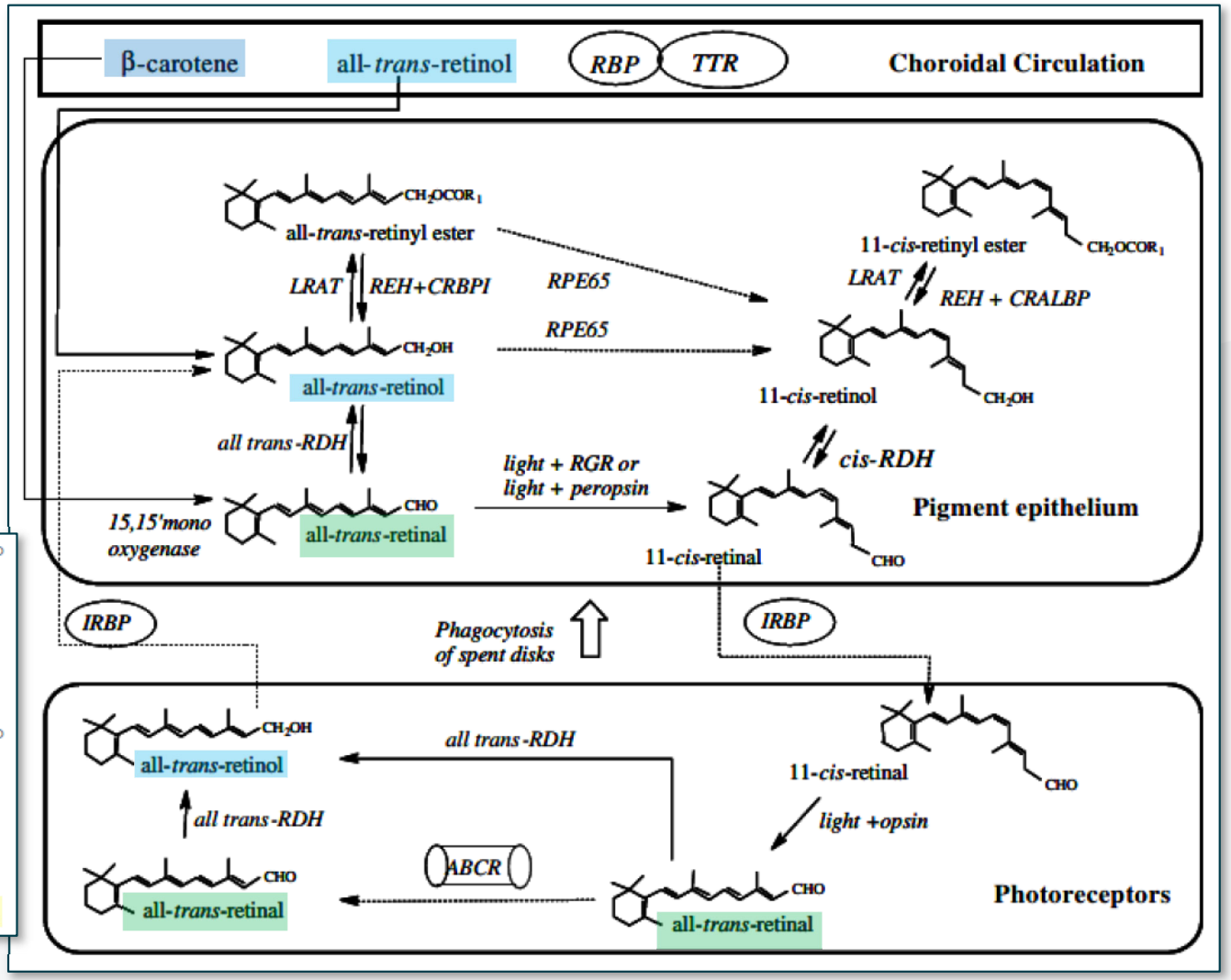
Q. You agree that vitamin A is essential to the visual cycle; correct?

A. I think that vitamin A is essential to the visual cycle.

Q. You agree that vitamin A is essential to the ability of human beings to see; correct?

A. I think that vitamin A is essential to the proper functioning of the retina into the visual cycle and that that is essential to vision.

EX1069 (Del Priore Depo. Tr.), 57:1-9.



EX1050, Fig. 1.

Pet., 8-10; Pet. Reply, 2-5; EX1002, ¶60.

Reason to Combine with Reasonable Expectation

A2E Is Not Required for Vision

73. 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).

EX1004 (Calman Decl.), ¶73.

B. It Was Known That a Byproduct of All-*trans* Retinal (ATR) Produced in the Visual Cycle Was Toxic AE2 Lipofuscin Associated With Macular Degeneration

78. By 2007, it was known that undesirable lipofuscin fluorophores associated with ophthalmic disorders including macular degeneration arise from A2E and all-*trans* retinal (ATR)-dimers that are formed as side effects of the visual cycle. In 2005, Nathan E. Fishkin, Janet R. Sparrow, Rando Allikmets, and Koji

EX1002 (Guengerich Decl.), ¶78.

Pet., 10-12; Pet. Reply, 2-5.

Reason to Combine with Reasonable Expectation

Trial Confirmed: A2E Is Not Required for Vision

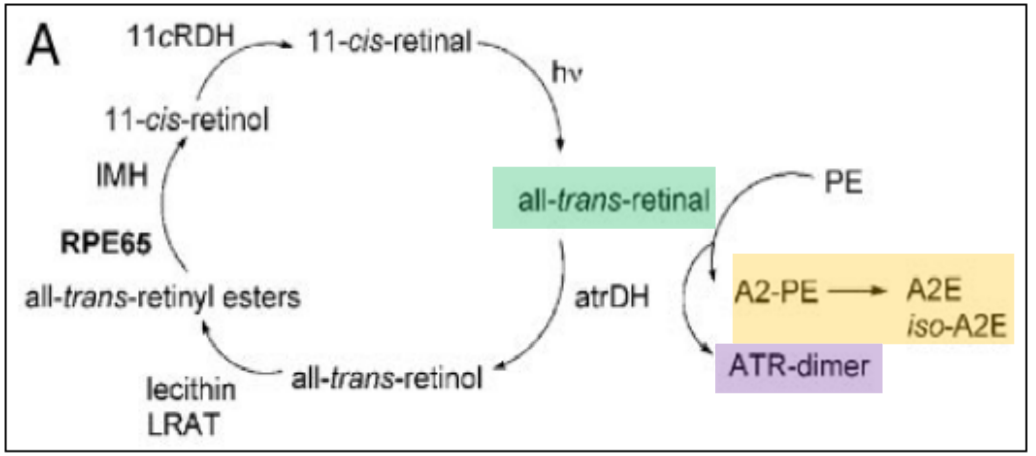


Figure 2. EX2058 (Kim 2004) at 1.

EX2052 (Prestwich Decl.), ¶56

A2E forms by non-enzymatic reactions in photo-receptor outer segments and RPE phagolysosomes, apparently as a minor and unavoidable by-product of the retinoid cycle[22,24,25] (FIG. 3a). In the presence of

EX2074 (Rattner 2006), 4

Q. Okay. So when there is a cycle that's essential for vision and then the A2E arm is something that if you could cut off, it's not going to impact the vision cycle; is that correct?

A. It should not impact the vision cycle.

EX1069 (Del Priore Depo. Tr.), 183:14-20

Q. And then it also depicts the formation of A2E as that arm, that side reaction you were talking about earlier; correct?

A. It does show the formation of A2E, yes.

Q. And the way it depicts A2E is that the A2E, it's an arm, it's a side reaction. It's not a necessary component of the visual cycle; do you agree?

A. So that is correct. That is the way they are depicting it.

EX1069 (Del Priore Depo. Tr.), 192:16-25

Pet., 10-12; Pet. Reply, 2-5.

Reason to Combine with Reasonable Expectation

Inhibited visual cycle predictably induced blindness

Blindness and corneal damage.

EX1019 (Furr), 596. Furr teaches that inadequate levels of vitamin A can lead to night blindness: "[n]ight blindness is a response to pronounced vitamin A deficiency." EX1019 (Furr), 596. In addition, Furr teaches that it was known that inadequate levels of vitamin A can lead to corneal damage. EX1019 (Furr), 596.

EX1002 (Guengerich Decl.), ¶71.

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),

EX1004 (Calman Decl.), ¶59.

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.

EX1004 (Calman Decl.), ¶58.

Pet., 8-10; Pet. Reply, 4-5, 13.

Reason to Combine with Reasonable Expectation

Inhibited visual cycle predictably induced blindness

Trial Confirmed: Cell death and irreversible loss of vision.

Q. And my question is specifically about photoreceptor cell death. So before September 2007, did ophthalmologists know that if you deprived the retina of vitamin A long term that that leads to photoreceptor cell death?

A. I think there was evidence that long-term vitamin A deprivation would lead to structural changes in the retina that might be irreversible, but I don't know how long that period of time is.

Q. And the structural changes in the retina that might be irreversible resulted in a loss of vision; is that correct?

A. Once you develop structural changes in the retina, you would have vision dysfunction associated with it.

EX1069 (Del Priore Depo. Tr.), 31:16-32:5.

Q. Do you see the sentence goes on to say, "Deficiency in vitamin A is well known to cause night blindness and eventual death of photoreceptors"?

A. Yes, I do see that.

Q. Do you agree with that portion of the sentence?

A. Yes, I do.

Q. And you agree that that was known to a person of ordinary skill in the art prior to September 2007?

A. Yes. I mean, this paper was in 1995.

EX1069 (Del Priore Depo. Tr.), 135:24-136:10.

Q. So here in paragraph 75 you testify that before September 2007 a person of ordinary skill in the art would have been aware that long-term slowing of the visual cycle leads to photoreceptor cell death and loss of vision; correct?

A. Yes.

Q. Do you stand by that testimony?

A. Yes, I do.

EX1069 (Del Priore Depo. Tr.), 216:20-217:2; *see also id.*, 31:16-24.

Pet. Reply, 4-5.

Reason to Combine with Reasonable Expectation

Inhibited visual cycle predictably induced blindness

Trial Confirmed: with vision cycle inhibition, "you get disease"; "severe loss of vision".

Q. What would happen if you inhibited the enzyme that converts all-trans-retinal to all-trans-retinol?

* * *

A. But generally speaking, if you interfere with this process, right -- first of all, there are diseases. You know, each of these enzymes, there are essentially diseases that occur because you've inhibited this step, and I'd have to refresh my memory and look at one of the actual exhibits to tell you which enzyme and which disease it is. But if you interfere at different steps, you get disease.

EX1069 (Del Priore Depo. Tr.), 45:10-25.

So basically, this is a retinol dehydrogenase and there is a mutation in that that's been found in people that causes a retinal degeneration called fundus albipunctatus.

Q. Is that disease also associated with loss of vision?

A. That disease is also associated with loss of vision, definitely.

EX1069 (Del Priore Depo. Tr.), 52:7-14.

A. So Leber congenital amaurosis is one of the diseases that occurs if you don't have efficient conversion of the all-trans-retinol inside the pigment epithelium cell.

Q. What are the characteristics of that disease?

A. Essentially this is a disease present at birth. It usually leads to severe loss of vision in children in a very young age. Patients develop loss of central vision and then night blindness. Most of the patients have lost significant if not all vision in child -- during childhood.

Q. That's as a result of inhibiting the visual cycle?

A. As a result of inhibiting the visual cycle, yes.

EX1069 (Del Priore Depo. Tr.), 49:19-50:9.

Pet. Reply, 4-5.

Reason to Combine with Reasonable Expectation

Inhibited visual cycle predictably induced blindness

Trial Confirmed: with visual cycle inhibitors, a variety of things can happen, none of which are good.

> So you need the integrity of this visual pathway in order for vision to function properly. If you interfere at any step, you are going to cause the next molecule not to be reduced and then a backup of the previous molecule or you may get deposition of abnormal molecules. There is a variety of things that can happen, none of which are good.

EX1069 (Del Priore Depo. Tr.), 46:17-24.

Pet. Reply, 4-5.

Reason to Combine with Reasonable Expectation

Inhibited visual cycle predictably induced blindness

Trial Confirmed: Detriments of visual cycle inhibition were predictable.

undesirable A2E formation. EX2052, ¶¶81-90. But none of Dr. Prestwich's discussion weighs against inhibiting the A2E byproduct pathway itself rather than the visual cycle. Yes, it was predictable that inhibiting the enzymes involved in the visual cycle (e.g., RPE65, 11cRDH, atRDH—Prestwich Figure 2) would lead to night blindness, delayed dark adaptation, and eventually cell death (and blindness), as I explained above. It also was predictable that inhibiting atRDH, which Dr. Prestwich repeatedly calls the "rate-limiting step," would **increase** A2E formation by reducing conversion of ATR to retinol. Prestwich Figure 2. EX2052, ¶¶60, 69-70 (atRDH reduces ATR to retinol); EX2052, ¶¶76, 84 (reduction of ATR to retinol "is the rate-limiting step in the vitamin A cycle"). However, none of Dr. Prestwich's questions about the visual cycle fairly call into question the wisdom of inhibiting the undesirable A2E byproduct pathway itself rather than the visual cycle.

EX1080 (Guengerich Reply Decl.), ¶67.

Pet., 8-10; Pet. Reply, 4-5, 13.

Reason to Combine with Reasonable Expectation

Visual cycle inhibition effective but impractical for therapy

Trial Confirmed: inhibits lipofuscin but "impractical as a potential treatment therapy".

Q. Right. So what this reference 2111 is telling us before September 2007 is that reducing dietary levels of vitamin A was impractical as a therapy for AMD and Stargardt macular dystrophy; correct? That's what it says.

A. What it's telling us is that the observation was made that reducing dietary levels of vitamin A in these disorders, you know, inhibit both lipofuscin and the autofluorescence accumulation, but they judge that impractical as a potential treatment or therapy.

EX1069 (Del Priore Depo. Tr.), 204:11-21.

Q. And you cite those references as teaching before September 2007 that slowing down the visual cycle causes delayed dark adaptation and night blindness; correct?

A. Yes, that's correct.

Q. Do you stand by your testimony in paragraph 74 that before September 2007 a person of order ordinary skill in the art would have known that treatment with isotretinoin or fenretinide will -- can slow down the visual cycle causing delayed dark adaptation and night blindness?

MR. FELDSTEIN: Object to form.

A. Yes.

EX1069 (Del Priore Depo. Tr.), 217:12-24.

Pet. Reply, 4-5.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Visual cycle inhibition effective but precluded as therapy

Adverse affects: "preclude long-term therapy"

Seizures, birth defects, depression, suicide

"Too toxic for long-term administration in humans"

Q. In paragraph 285, you rely on a 2005 reference by Radu for the proposition that fenretinide was known to cause delayed dark adaptation and other side effects.

Do you see that?

A. Yes, I do.

Q. Do you stand by that testimony?

A. Yes, I do.

Q. You also rely on a 2004 reference by Puduvalli for the proposition that patients treated with fenretinide experienced a variety of symptoms including seizure and confusion.

Do you see that?

A. Yes, I do.

Q. You agree that all of these side effects would have been known to a person of ordinary skill in the art prior to September of 2007?

A. Yes, I do.

Q. You stand by that testimony?

A. Yes, I do.

EX1069 (Del Priore Depo. Tr.), 215:17-216:11.

EX1069, 214:13-20.

Q. In paragraph 284 you testify that isotretinoin, also known as Accutane, was considered too toxic for long-term administration in humans.

Do you see that?

A. Yes, I do.

Q. Do you stand by that testimony?

A. Yes.

EX1069, 214:21-215:11.

Q. You also testified that the danger of side effects in humans, such as birth defects in pregnant women and depression and suicide reported in many cases of isotretinoin treatment would preclude long-term therapy with this drug.

Do you see that?

A. I do see that, yes.

Q. And you cite the Wolf 2003 reference for that?

A. I do.

Q. You agree that that information was available to a person of ordinary skill in the art before September 2007; correct?

A. I do. The Wolf paper was 2003.

Q. And you stand by this testimony?

A. Yes, I do.

Pet. Reply, 4-5.

Reason to Combine with Reasonable Expectation

The literature called for alternatives to visual cycle inhibition

- Serious adverse effects of visual cycle inhibition (*see* slides 34-40 above)
- Literature suggested specifically inhibiting A2E formation instead of inhibiting visual cycle (see slides 28-33 above).
  - Mata
  - Kim 2007
  - Howes

eration. Pharmacologic 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 (Mata), 7159.

Improved understanding of the mode of genesis of A2E and other RPE lipofuscin compounds could facilitate the introduction of yet other novel approaches to therapy. In previous studies we corroborated several steps in the formation of A2E. Here, in work aimed at the further

EX2019 (Kim 2007), 7.

Q. Well, so let's start with: This is a reference from what year? This is from September 2006; is that correct?

A. Yes, that is correct, 2006.

Q. So as of the beginning of September 2007, you agree that a person of ordinary skill in the art would have been aware that recent efforts for treating AMD and Stargardt macular dystrophy have centered on targeting A2E formation in RPE cells as a therapeutic strategy for AMD and AMD-like retinal disorders; correct?

* * *

A. Yes.

EX1069 (Del Priore Depo. Tr.), 203:2-14 (citing EX2111 (Howes)).

oxidation of a dihydropyridinium intermediate dihydro-A2PE. An understanding of the biosynthetic pathways of retinal pigment epithelial lipofuscin pigments is critical to the development of therapies for macular degeneration that are based on limiting the formation of these damaging compounds.

EX2019 (Kim), Abstract.

Pet. 2, 18, 31, 40, 42, 44, 48, 54, 58, 67; EX1002, ¶¶97, 179, 181, 221, 244; Pet. Reply, 2-5; EX1080, ¶¶31-32; slide 59.

Literature Optimistic about Slowing MD Progression

Trial Confirmed: Lipofuscin drusen deposits are reversible

Dynamic "balance between deposition and clearance" provides "good reasons to be optimistic"

Slowing progression "as little as 10-20%" provides "substantial" impact on health

Current evidence suggests that at least some sub-RPE deposits have a dynamic natural history in which accumulation reflects a balance between deposition and clearance. For example, fundus photographs taken several years apart often show both the appearance of new drusen and a regression of older ones[52,53]. In the Beaver Dam Eye Study, 12% of eyes with 'soft' drusen at the time of enrolment showed no drusen 5 years later[53].

EX2074 (Rattner), 5-6.

work. The trend of current research suggests that, as we learn more about the pathophysiology of the macular degenerations, we might be able to view them increasingly as disorders of homeostasis. If this is the case, then there are good reasons to be optimistic. If retinal, RPE or immune system physiology can be modified by a treatment that slows the rate of disease progression by as little as 10–20%, and thereby delays the onset of vision loss by 5–10 years, the impact on human health will be substantial.

EX2074 (Rattner), 11.

Pet. Reply, 22; EX1080, ¶72.

Literature Optimistic about Slowing MD Progression

Trial Confirmed: Lipofuscin drusen deposits are reversible

"A dynamic process where deposits" can "come and go and change over time"

"They really do come and go"

Q. So in the bottom of the right-hand page of 864 of Exhibit 2074, where it says, "at least some sub-RPE deposits have a dynamic natural history in which accumulation reflects a balance between deposition and clearance," do you have an understanding as to what that means?

A. I have an understanding of what they are referring to, yes.

Q. What is that?

EX1069 (Del Priore Depo. Tr.), 193:25-195:2 (quoting EX2074) (continued, excerpt on right).

resolved. So what is clear is that the drusen are dynamic. They are not just, you know, stamped in a brick like an old Roman stamping and stay there forever. They really do come and go.

EX1069 (Del Priore Depo. Tr.), 196:4-7.

A. Essentially what they are meaning in my view from that sentence is if the sub-RPE deposits, which are proteins and lipids that are outside the cell, they're sort of wound up in the mortar underneath the cells, that those are dynamic and not static. If they were static, those deposits would be there and they would never resolve and the patient would accumulate other deposits, but the originals ones aren't going away.

What's actually seen in patients is a dynamic process where the deposits, which can be seen on photographs and OCT imaging, they are called drusen, d-r-u-s-e-n, that those can come and go and change over time. So patients can have deposits in one area, have a picture taken five years later, ten years later; some of those deposits are still there, some are gone, some new ones have formed. And five years later the same part happens.

EX1069 (Del Priore Depo. Tr.), 193:25-195:2 (discussing EX2074).

Pet. Reply, 22; EX1080, ¶72.

Reason to Combine with Reasonable Expectation

Deuterium KIE in POSA's toolkit

Slowing undesirable reactions involving C-H bond cleavage – "profound effect" of 7-10 times

100. Using deuteration to slow undesirable reactions was one of several known uses of deuteration by 2007. For example, it was known that: (i) deuteration of a compound was useful for tracking compounds in vivo; (ii) the deuteration of a compound was useful for the identification of metabolites and sites of metabolic action; and (iii) the deuteration of a compound was useful for the inhibition (e.g., slowing) of reactions that involve cleavage of a carbon-hydrogen bond.

EX1002 (Guengerich Decl.), ¶100.

Haskins states:

> The difference in mass between deuterium and protium causes the vibrational frequencies of C – D, O – D and N – D bonds to be lower than for corresponding C – H, O – H and N – H bonds. The more stable deuterium bond requires greater energy of activation and substitution of deuterium for protium can have ***a profound effect on the rate of chemical reactions involving bond cleavage***.

EX1012 (Haskins), 273. Haskins thus explains that deuterium substitution can have a profound effect on the rate of chemical reactions involving bond cleavage.

EX1002 (Guengerich Decl.), ¶108.

109. Haskins further discloses that the rate of bond cleavage for a deuterium is generally 2-5 times slower than for the hydrogen, but can be as high as 7- to 10-fold slower. For example, Haskins states that "[g]enerally values k_H/k_D are in the range of 2-5, but the maximum effect can be as high as 7-10." EX1012 (Haskins), 273. Reducing the speed by 2-10 times of a reaction requiring cleavage of a carbon-hydrogen bond was thus an expected result.

EX1002 (Guengerich Decl.), ¶109.

Pet., 12-15, 40-43.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Deuterium KIE in POSA's toolkit

PO's expert: "versatile tool" to improve drugs by slowing or redirecting enzymatic metabolism

> 129. As of September 2007, the deuterium kinetic isotope effect was recognized as a versatile tool for studying chemical and biological processes. Its applications in these fields included analytical techniques like mass spectrometry, pharmacokinetic studies, metabolic investigations, mechanistic studies, structural elucidation, and isotope tracing, to name but a few. *See generally* EX1013 (Baillie); EX1047 (Blake) at 1;[33] EX1046 (Kushner 1999) at 1, 5–7.[34]

EX2052 (Prestwich Decl.), ¶129.

> 139. At the time of invention, researchers had also attempted to use deuterium substitution to improve drugs by slowing or redirecting their enzymatic metabolism. *E.g.*, EX1012 (Haskins) at 1–2; EX1051 (Miwa) at 1. Drs. Guengerich

EX2052 (Prestwich Decl.), ¶139.

Pet. Reply, 12-15, Pet., 12-15, 40-43.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Deuterium KIE in POSA's toolkit

Deuterium KIE: stabilize known active while reducing undesirable, toxic byproduct

segment."); EX1036 (Fishkin 2003), 2. A POSA would have understood from Mata, Kim 2007, and other references that the [1,5]-shift unleashes the conversion of the essential vitamin A nutrient into a toxic and undesirable byproduct. A POSA would have reasonably expected C_{20}-deuteration to thus preserve the vitamin A nutrient (analogous to stabilizing the desired drug for a prolonged, desired effect) while also reducing production of the undesirable, toxic byproduct (analogous to metabolic switching). C_{20}-deuteration of vitamin A thus fits well within the established paradigm of improving existing compounds through targeted deuteration.

EX1080 (Guengerich Reply Decl.), ¶48; *see also* EX1002 (Guengerich Decl.), ¶¶257-264.

Pet. Reply, 3, 14-15, 22; Pet., 40-43.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Deuterium KIE in POSA's toolkit

C_{20}-D_3 vitamin A: well-within the established deuterium KIE paradigm

of the essential vitamin A nutrient into a toxic and undesirable byproduct. A POSA would have reasonably expected C_{20}-deuteration to thus preserve the vitamin A nutrient (analogous to stabilizing the desired drug for a prolonged, desired effect) while also reducing production of the undesirable, toxic byproduct (analogous to metabolic switching). C_{20}-deuteration of vitamin A thus fits well within the established paradigm of improving existing compounds through targeted deuteration.

49. By inhibiting the [1,5]-shift, the NRPE would remain available for active transport in cells with functioning ABCR transporters (e.g., in AMD patients), for conversion back to retinol (and subsequent use in the visual cycle), and for passive transport even in cells without functioning ABCR transporters.

EX1080 (Guengerich Reply Decl.), ¶¶48-49.

Pet. Reply, 14-15; Pet., 40-43.

Reason to Combine with Reasonable Expectation

Reasonably likely to attenuate A2E formation

Dr. Guengerich consistently testified **C_{20}-Deuteration:**
"would materially slow"; "easiest route to inhibition"

analogues. As I explain in great detail below, a person of ordinary skill in the art would have understood from Mata's disclosure of the biosynthetic pathway for A2E formation that replacing the C_{20} hydrogens with deuterium would materially slow the formation of A2E. Accounting for the disclosures of Olson 1988, Mata, and Widder, as well as well-known teachings about the primary kinetic isotope effect (KIE) and the use of selective deuterium substitution of pharmaceutical compounds to slow reactions involving removal of a hydrogen at a particular position (as even noted by the patent applicant during prosecution), it is my opinion that claims 1-54 in the challenged '045 patent would have been obvious before the critical date of September 2007.

EX1002 (Guengerich Decl.), ¶50.

It turns out that the 1,5-sigmatropic rearrangement presents what I -- what I think a POSA would consider the easiest route to inhibition because all one had to do was introduce the different isomer of hydrogen at a particular position, which was already known and reported in the literature.

EX2103 (Guengerich Depo. Tr.), 65:8-14.

As such, it is my opinion that the prior art references disclosed herein supports the reasonable expectation that C_{20}-deuteration of vitamin A would slow A2E/lipofuscin formation by 5-10 times.

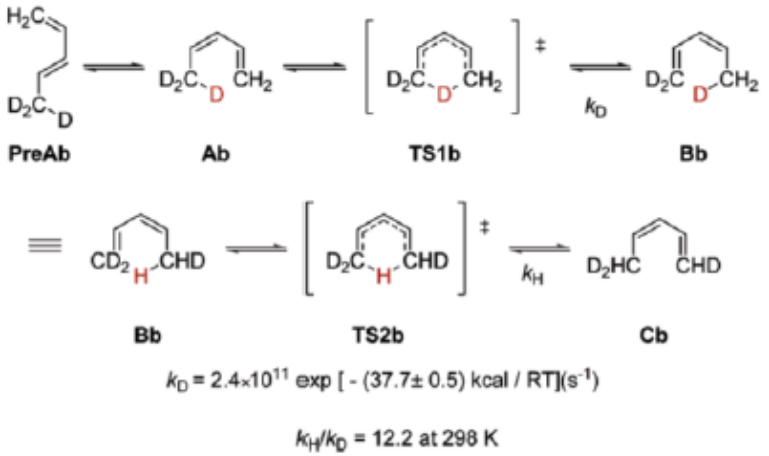
EX1002 (Guengerich Decl.), ¶269.

Pet., 12-15, 40-46; Pet. Reply 5-7, 10.

Reason to Combine with Reasonable Expectation

Reasonably likely to attenuate A2E formation

Roth and Itou support reasonable expectation of success



118. Itou further discloses that the authors in the Roth article experimentally determined a large kinetic isotope effect value of 12.2 in a 1,5-sigmatropic shift of a deuterated 1,3-pentadiene. For example, Itou states that:

> *The large KIE value of k_H/k_D = 12.2* (k_H and k_D refer to the rate constant of the reaction for H and D compounds, respectively) at 298 K, which is derived from the extrapolation from the values in the temperature ranging 463.4-478.5 K and modified intermediate neglect of differential overlap (MINDO)/2 calculations, suggests that the reaction proceeds according to a mechanism that includes a transition structure with CS symmetry

EX1016 (Itou), 261.

EX1002 (Guengerich Decl.), ¶¶117-118.

120. Roth discloses measuring and comparing the gas-phase reaction of (*Z*)-1,3-pentadiene and deuterated (*Z*)-1,3-pentadiene. The mechanism proposed in Roth is outlined in Figure 2 of Itou, which I have reproduced above.

121. Roth disclosed that there is a large kinetic isotope effect value (e.g., 12.2) associated with the 1,5-sigmatropic shift in diene systems. Specifically, Roth determined experimentally that the 1,5-sigmatropic shift of a deuterated 1,3-pentadiene (with a CD_3) would proceed 12.2 times slower than the protiated 1,3-pentadiene.

122. As such, a person having ordinary skill in the art would expect that the substitution of the C_{20} methyl (CH_3) with CD_3 would similarly observe a large kinetic isotope effect associated with the 1,5-sigmatropic shift at the C_{20} position. Further, it is my opinion that deuteration of the C_{20} methyl would have a similar kinetic profile as the well-studied 1,3-pentadiene system outlined in both Roth and Itou because C_{20} forms a similar diene system as in 1,3-pentadiene.

EX1002 (Guengerich Decl.), ¶¶120-122.

Pet., 12-15, 42-43, 67-68.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Reasonably likely to attenuate A2E formation

Dr. Guengerich confirmed: You'll actually have less material regardless of how slow or fast subsequent steps are

THE WITNESS: As I said, you can have multiple slow steps, and I'd also like to make a point that this is a little -- somewhat different than what we see in normal enzyme reactions.

These are strictly chemical reactions, and in many ways, they're actually simpler. So if you inhibit the first step, which is the one involved -- well, effectively, the first step after the condensation of the phosphatidyl at the nolamine, if you inhibit that step, you will block the accumulation of the APE intermediate, and then you'll actually have less material to go on to the subsequent products, regardless of how slow or fast they are.

EX2103 (Guengerich Depo. Tr.), 57:22-58:12

Pet., 41-42, 67; Pet. Reply, 2, 5-7.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Reasonably likely to attenuate A2E formation

Deuterium KIE where C-H bond breakage at least partially rate-limiting

or FDA approval. EX1070, 59:22-66:6. Moreover, Dr. Prestwich ignores testimony that Patent Owner's counsel submitted in this case explaining that it has been understood for many decades to use targeted deuterium substitution to slow C-H bond breakage on biological or pharmaceutical compounds to improve safety and/or efficacy where the C-H bond breakage was at least partially rate-limiting. EX2008, 25-27. Patent Owner's counsel submitted testimony that deuterium substitution was expected to maintain a compound's selectivity and potency. EX2008, 31. In the scenario at issue here, that means that C_{20}-deuterated vitamin A was expected to favorably support the essential ocular functions of vitamin A (including the visual cycle) while decreasing the amount of undesirable A2E/lipofuscin formed. It was thus a predictable result to a POSA that C_{20}-deuterated vitamin A substitution would reduce A2E/lipofuscin formation without interfering with the visual cycle.

EX1080 (Guengerich Reply Decl.), ¶12; *see also* EX1002 (Guengerich Decl.), ¶¶99-123, 60, 98.

Pet. Reply, 15; Pet., 40-43.

Reason to Combine with Reasonable Expectation

Trial Confirmed: Reasonably likely to attenuate A2E formation

Patent admits efficacy naturally results from C_{20}-deuteration:

absent. FIG. **3**C is a plot of A2E formation over time for the above reactions. C_{20}-D_3-all-trans-retinal forms A2E about 7-times slower than all-trans-retinal.

EX1001, 6:35-37.

visual effects. When C_{20} hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. **3**) and ATR-dimer formation is about 15 times slower (FIG. **4**).

EX1001, 8:32-34.

Replacing the C_{20} Hydrogens of All-Trans-Retinal with Deuteriums Slows the Formation of A2E-Lipofuscin in CD-1 (ICR) Mice

EX1001, Example 3.

Pet., 35-36; Pet. Reply, 15-17.

WILSON
SONSINI

Patent Owner's Response Arguments

Patent Owner's Response Arguments

- ***Argues Drs. Guengerich and Calman are not POSAs***
- ***Argues Teaching away from vitamin A for macular degeneration patients***
- ***Argues 1,5-shift may be not the only rate-limiting step***
- ***Argues Mowery and Verdegem undermine Roth and Itou's Strong KIE***
- ***Hypothesizes 1,5-shift is enzymatic- or general-acid-base- catalyzed rather than sigmatropic rearrangement***
- ***Argues Secondary considerations***

POR, PO Sur-Reply.

Dr. Calman Qualified POSA

Dr. Calman not a mere "generalist":

- Dr. Calman is well-qualified
  - Diagnoses and treats patients with retinal and macular disease; diagnoses Stargardt. EX2104, 10:21-12:11.
  - "Half of my patients have retinal or macular disease" EX1004, ¶¶5-10.

> A. I'm an ophthalmologist who diagnoses and treats patients with macular disease. That said,

EX2104 (Calman Depo. Tr.), 11:17-18.

Referring Stargardt patients for treatment not disqualifying:

- PO attacks Dr. Calman because he refers Stargardt patients to a colleague for care.
- PO's clinician behaves similarly.

> Q. Are there any lifestyle modifications that would have been offered to the patient as advice to attempt to ameliorate the Stargardt syndrome?
>
> **A. That would have happened after I saw them. I would not usually talk to patients about that because I always refer them to another retinal specialist afterwards.**

EX1069 (Del Priore Depo. Tr.), 266:3-10.

Pet., 6-7; Pet. Reply, 26-27; EX1002, ¶¶2-12; EX1003; EX1004, ¶¶2-10; EX1005; EX2104, 10:21-12:11.

Dr. Guengerich Qualified POSA

Dr. Guengerich's expertise satisfies both parties' definitions.

- Ph.D., Biochemistry
- Publications in retinoid and steroid biochemistry and deuteration

Q. Are steroids terpenes?

A. Steroids, in fact, are also terpenes.

EX1070 (Prestwich Depo. Tr.), 28:11-12.

Q. Now, earlier, we were talking about the definition of a POSA in paragraph 26 of your declaration. Do you recall that?

A. Yes.

Q. And you testified that you are a POSA under that definition, that you have not offered any opinion that Dr. Guengerich is not a POSA under that definition. Am I correct so far?

A. I believe that's what our conversation was.

* * *

Q. Are you offering an opinion in this case that Dr. Guengerich is not a POSA under the definition that you identify in paragraph 28 of your declaration?

* * *

THE WITNESS: I don't see where I offer any such opinion.

EX1070 (Prestwich Depo. Tr.), 53:18-55:2.

Pet., 6-7; Pet. Reply, 27.

No teaching away from C_{20}-Deuterated Vitamin A

- Improper piecemeal attack on individual references.
- No showing of active discouragement from the proposed combination.
  - Vitamin A commonly and safely administered to AMD patients (see slides 12-21 above)
  - ABCR-linked disease tied to specific ocular locus, not highly-regulated serum concentrations.

Q. So in the sentence, you say, "in the absence of rim protein, NRPE and ATR accumulate in the disc interior." Do you see that?

A. Yes.

Q. So they accumulate in the disc interior, thus providing the excess ATR believed to be the substrate for A2E formation in Mata's proposed pathway, correct?

A. Believed to be the substrate for the A2E formation. Yes, that's what I heard.

Q. So the location we are discussing in this sentence is the disc interior, correct?

A. That's what we are discussing in that sentence, yes.

EX1070 (Prestwich Depo. Tr.), 111:8-21.

96. One of skill in the art would have recognized that the ROS and RPE are decidedly different cellular environments. The ROS environment is characterized by a neutral pH and a reducing atmosphere maintained to protect against oxidative stress. In contrast, the RPE, particularly within its lysosomes, comprises an acidic

EX2052 (Prestwich Decl.), ¶96 (ROS = Rod Outer Segment).

69. Dr. Prestwich appears to agree that NRPE formation and the condensation of NRPE with a second ATR molecule both occur in the neutral environment of the disc space of the photoreceptor outer segments, but questions whether the dihydro-A2PE and A2PE intermediates and the A2E product form primarily in this same neutral environment or only subsequent to RPE-phagocytosis of the photoreceptor cells. EX2052, ¶¶91-97, 100 (FN21), 103

EX1080 (Guengerich Reply Decl.), ¶69.

Pet. Reply, 2, 11.

No teaching away from C_{20}-Deuterated Vitamin A

PO's submitted prior art confirms motivation to inhibit A2E specifically and save the visual cycle

In the development of novel approaches to treatment of macular degeneration, attention has been given to approaches that reduce the formation of RPE lipofuscin pigments (3-5,8). Improved understanding of the mode of genesis of A2E and other RPE lipofuscin compounds could facilitate the introduction of yet other novel approaches to therapy. In previous studies

EX2019 (Kim), 7.

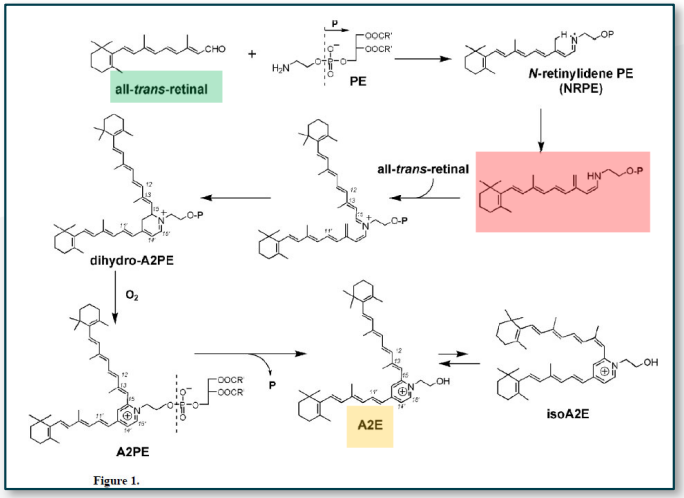
3. Maiti P, Kong J, Kim SR, Sparrow JR, Allikmets R, Rando RR. Small molecule RPE65 antagonists limit the visual cycle and prevent lipofuscin formation. Biochem 2006;45:852–860. [PubMed: 16411761]

4. Sieving PA, Chaudhry P, Kondo M, Provenzano M, Wu D, Carlson TJ, Bush RA, Thompson DA. Inhibition of the visual cycle in vivo by 13-cis retinoic acid protects from light damage and provides a mechanism for night blindness in isotretinoin therapy. Proc Natl Acad Sci U S A 2001;98:1835–1840. [PubMed: 11172037]

5. Radu RA, Mata NL, Nusinowitz S, Liu X, Sieving PA, Travis GH. Treatment with isotretinoin inhibits lipofuscin and A2E accumulation in a mouse model of recessive Stargardt's macular degeneration. Proc Natl Acad Sci U S A 2003;100:4742–4747. [PubMed: 12671074]

8. Radu RA, Han Y, Bui TV, Nusinowitz S, Bok D, Lichter J, Widder K, Travis GH, Mata NL. Reductions in serum vitamin A arrest accumulation of toxic retinal fluorophores: a potential therapy for treatment of lipofuscin-based retinal diseases. Invest Ophthalmol Vis Sci 2005;46:4393–4401. [PubMed: 16303925]

EX2019 (Kim), 8.



EX2019 (Kim), 10.

oxidation of a dihydropyridinium intermediate dihydro-A2PE. An understanding of the biosynthetic pathways of retinal pigment epithelial lipofuscin pigments is critical to the development of therapies for macular degeneration that are based on limiting the formation of these damaging compounds.

EX2019 (Kim), Abstract.

Pet. Reply, 2-5; EX1080 (Guengerich Reply Decl.), ¶¶31-32; *see also* slide 41.

1,5-Shift Need Not Be Sole Rate-Limiting Step

Dr. Guengerich Repeatedly Testified

A POSA would recognize the 1,5-shift likely was a rate-limiting step

- Mata "provides good reason to believe that lipofuscin is formed by removal of a hydrogen from the C_{20} of prior art vitamin A analogues and that pharmacologically inhibiting this synthesis pathway will slow lipofuscin formation and may provide an effective treatment for macular degeneration." EX1002 (Guengerich Decl.), ¶48.
- "[S]ubstituting deuterium in place of the hydrogens at C-20 would slow A2E formation due to the high primary kinetic isotope effect expected from this substitution" *Id.*, ¶260.
- "Mata further discloses that this synthetic pathway depends on removing a hydrogen atom from C_{20} through a 1,5-sigmatropic shift." *Id.*, ¶261.
- "During my deposition, I again explained that a POSA would have recognized from viewing the biosynthetic pathways in Mata that the 1,5-sigmatropic rearrangement was likely 'a' rate-limiting step in the overall process, that requiring identification of 'the' one and only rate-limiting step was unnecessary for this pathway, and that a POSA would have recognized that slowing the 1,5-sigmatropic rearrangement likely would slow the production of A2E regardless of whether any other steps identified by Mata also could be inhibited to slow A2E production." EX1080 (Guengerich Reply Decl.), ¶18.
- "Contrary to the Patent Owner's argument, I did not abandon my opinion that a POSA would have recognized C-20 deuteration was likely to inhibit the 1,5-sigmatropic rearrangement and thereby favorably inhibit A2E formation, regardless of whether inhibiting subsequent steps (e.g., the 3,3-sigmatropic rearrangement) also was likely to slow A2E formation to some extent." EX1080, ¶19.

Pet., 41-42, 67; Pet. Reply, 5-7; EX1002, ¶¶259-260.

1,5-Shift Need Not Be Sole Rate-Limiting Step

Dr. Guengerich Repeatedly Testified

"Simpler" "strictly chemical reaction"; "it doesn't matter if the subsequent steps are slow"
You'll actually have less material "regardless of how slow or fast" subsequent steps are
"block the 1,5-sigmatropic rearrangement, you will block everything"

THE WITNESS: As I said, you can have multiple slow steps, and I'd also like to make a point that this is a little -- somewhat different than what we see in normal enzyme reactions.

These are strictly chemical reactions, and in many ways, they're actually simpler. So if you inhibit the first step, which is the one involved -- well, effectively, the first step after the condensation of the phosphatidyl at the nolamine, if you inhibit that step, you will block the accumulation of the APE intermediate, and then you'll actually have less material to go on to the subsequent products, regardless of how slow or fast they are.

EX2103 (Guengerich Depo. Tr.), 57:22-58:12

I've answered that. I guess the point is that it doesn't matter if the subsequent steps are slow if you can actually inhibit the first one. Or I should say attenuate the first one. Then you will actually lead to less of a final product.

EX2103 (Guengerich Depo. Tr.), 63:19-25.

A. I think the point in my report is that basically, if you block the 1,5-sigmatropic rearrangement, you will block everything downstream, and some of the fine details of exactly how that happened may not be an issue because you're going to block everything.

EX2103 (Guengerich Depo. Tr.), 106:9-14.

Pet. Reply, 5-7; PO Sur-Reply, 3.

1,5-Shift Need Not Be Sole Rate-Limiting Step

Dr. Guengerich explained

Reaction rate in linear chain depends on reactant concentration supplied by earlier step

22. Dr. Prestwich's assertion depends on a flawed assumption that the reaction rate of one step in a linear chain of reactions is unaffected by the rate of the steps that precede it. As Dr. Prestwich admits elsewhere, however, a reaction rate often increases as the concentration of the reactants increases. EX2052, ¶184

* * *

23. The reaction rate will similarly decrease as the concentration of the reactants decreases. This fact is evidenced by Dr. Prestwich's assertions that restricting ATR from the eye would reduce A2E concentration (multiple steps downstream from ATR in the biosynthesis pathway for the A2E byproduct). EX2052, ¶¶50, 56. This example also amply demonstrates the error of assuming a reaction must be "the Rate-Limiting Step" in a pathway to impact the concentration of the ultimate product. The creation of ATR in the visual cycle is a

EX1080 (Guengerich Reply Decl.), ¶¶22-23.

Pet. Reply, 6-7.

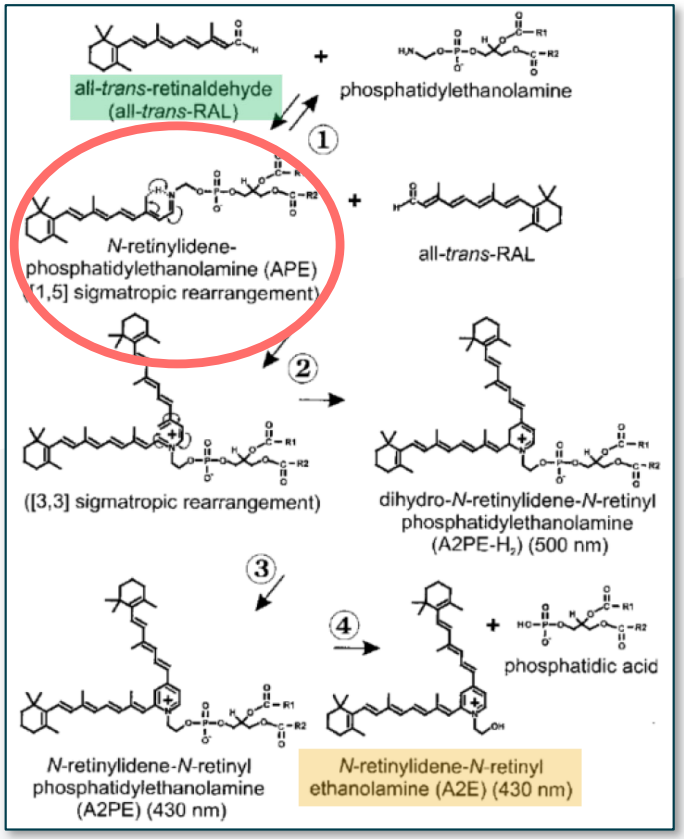
1,5-Shift Need Not Be Sole Rate-Limiting Step

Dr. Guengerich explained

Bimolecular condensation points to 1,5 shift because the **activated ATR** is the limiting reactant.

42. First, Dr. Prestwich argues that a POSA would have looked to inhibit the bimolecular condensation of NRPE with a second ATR molecule by limiting the ATR concentration in the outer segment. EX2052, ¶¶197-206. Dr. Prestwich reasons that the rate of the bimolecular reaction would be multiply-dependent on ATR concentration and would be unlikely to occur frequently in a complex, chiral protein-lipid membrane environment. But Dr. Prestwich's point that ATR concentrations in the disc space of the photoreceptor outer segment were elevated points in the opposite direction than what he says: it indicates that the phosphatidyl analogue of enamine (via C_{20}-deuteration) is the limiting reactant. Reducing the concentration of the limiting reactant (in this case, inhibiting the [1,5]-shift) would predictably slow the biomolecular condensation and the downstream, irreversible, and undesirable formation of dihydro-A2PE more potently and easier than reducing ATR concentrations, and without the predictable and undesirable adverse effects on vision that resulted from reducing ATR formation.

EX1080 (Guengerich Reply Decl.), ¶42.



EX1010 (Mata), Fig. 5.

Pet. Reply, 9-10.

1,5-Shift Need Not Be Sole Rate-Limiting Step

Dr. Guengerich explained

Linear reaction: everything will slow down if you block the 1,5-shift

Q And what is your opinion in regards to the synthesis pathway for A2E in regards to whether the 1,5 shift needs to be the slowest step as opposed to a rate-limiting step in the pathway?

A I think for a success -- for it to see -- to have a successful outcome here due to deuteration, it can be one of the rate-limiting steps, but it does not have to be the rate-limiting step.

Q And why is that the case?

MR. CHRISTIE: Objection.

THE WITNESS: Well, it's a linear reaction. And if you block the -- slow down the first reaction, everything will pile up beyond that -- or I should say slow down would be a better term than pile up.

EX2209 (Guengerich 2nd Depo. Tr.), 141:16-142:8

- ***Record here*** supports large expected KIE.
  - Slides 44-52, above.
- Simple, linear chemical pathway

Pet. Reply, 3-4; PO Sur-Reply, 4; Paper 13, 49 n.29

1,5-Shift Need Not Be Sole Rate-Limiting Step

PO's Rate-Calculation Arguments Fail

Calculating rates was **not required**:

- Guengerich: Mata provides information sufficient to reasonably expect [1,5]-shift was ***a*** rate-limiting step. EX1080, ¶25.
- Practice was to ***measure*** KIE effect, not ***calculate*** rate constants in advance. *Id.*, ¶26.
- Rate constant varies with concentration; "cumbersome task" to calculate and measure rate constants and concentrations. *Id.*

> 2000's proposed A2E pathway." EX2052, ¶¶110-111, 158, 160, 179-195. As I explained above, however, there was no need to identify a sole and exclusive ("the") rate-limiting step and no need to calculate the rates of all individual reaction steps *a priori*. The information presented by Mata was sufficient for a POSA to have a reasonable expectation that the [1,5]-shift was "a" rate-limiting step.

EX1080 (Guengerich Reply Decl.), ¶25.

Pet. Reply, 7.

1,5-Shift Need Not Be Sole Rate-Limiting Step

PO's Rate-Calculation Arguments Fail

PO's masking argument is speculative, at most goes to degree of KIE observed.

- Even if masking present, POSA would reasonably expect A2E/lipofuscin formation would slow
  - linear and essentially non-enzymatic pathway
  - Significant susceptibility of 1,5-shift to very strong KIE
- POSA would readily use KIE studies to measure the inherent KIE that results from C20-substitution.

54. Dr. Prestwich testifies about KIE masking (primarily in enzymatic cycles). E.g., EX2052, ¶¶136-138, 259-262. Because of the pathway at issue here (which is both linear and essentially non-enzymatic), the nature of the [1,5]-shift, and its significant susceptibility to a very strong KIE, masking would not undermine the reasonable expectation of success. Dr. Prestwich's masking argument is speculative, and at most goes to the degree of the KIE that would be observed when measuring A2E rather than whether a KIE likely would result. As I explained previously, and as admitted by the patent, the KIE measured in the challenged patent is the natural result of the C_{20}-deuteration, which was already disclosed in the prior art. A POSA thus would have had a reasonable expectation of success for reducing A2E/lipofuscin formation based on the information available before September 2007. The ease with which this reasonable expectation would have been easily confirmed using routine kinetic isotope studies, as even Dr. Prestwich agrees, demonstrates that it was a straightforward matter (i.e., there was no technical barrier) and there was a low bar for a POSA to provide experimental data for the substitution.

EX1080 (Guengerich Reply Decl.), ¶54.

Pet. Reply, 13.

Literature Precedents Supports Substitution

Trial Confirms: Roth and Itou Support Strong Expected KIE

"Forced" conditions required to speed up slow reaction

53. Like Roth, Doering could not observe the 1,5-sigmatropic rearrangement under physiological conditions because it was simply too slow of a reaction. Like Roth, Doering thus forced the reaction (339 days at elevated temperatures including 98.4 °C). EX2025, Abstract, 9084. Fishkin and Mata similarly had to force "a slow reaction" that was not very efficient under physiological conditions. EX2103, 120:6-19; EX2103, 123:2-6 ("they are not what I call physiological conditions. I think my opinion would be that these conditions were actually used to force the reaction to make these products"), 124:8-21 (Roth & Konig and subsequent material published since then, but before the patent—namely Doering (EX2025)— recognized that cleavage of the referenced carbon-hydrogen bond would have been slow under physiological conditions), 61:24-62:2 ("Itou and…D[oe]ring later on talked about…basically it's an irreversible step"), 73:6-74:4 ("there's another experimental study later by D[oe]ring as well"), 75:5-6 ("I think there were more than one in D[oe]ring, actually, as I recall"). Accordingly, both the nature of the reaction and its position in the pathway made it a prime and favorable location to inhibit lipofuscin formation, as I explained repeatedly before. A priori calculations of the specific rate constants of the various

EX1080 (Guengerich Reply Decl.), ¶53.

Pet. Reply, 7-8.

Literature Precedents Supports Substitution

Trial Confirms: Roth and Itou Support Strong Expected KIE

Extreme conditions required to speed up slow reaction

> Doering, a 2006 publication that the Patent Owner submitted in this case, corroborated the teachings of Roth and Itou that a large KIE was expected for the 1,5-sigmatropic rearrangement (disclosed in Mata). EX2025. Where Roth reported a KIE of 12.2, Doering, the reference Patent Owner submitted, taught that—at room temperature—the KIE would be even larger (16.6).

EX1080 (Guengerich Reply Decl.), ¶52.

> 53. Like Roth, Doering could not observe the 1,5-sigmatropic rearrangement under physiological conditions because it was simply too slow of a reaction. Like Roth, Doering thus forced the reaction (339 days at elevated temperatures including 98.4 °C). EX2025, Abstract, 9084. Fishkin and Mata similarly had to force "a slow reaction" that was not very efficient under physiological conditions. EX2103, 120:6-19; EX2103, 123:2-6 ("they are not what I call physiological conditions. I think my opinion would be that these conditions were actually used to force the reaction to make these products"), 124:8-21 (Roth & Konig and subsequent material published since then, but before the patent—namely Doering (EX2025)— recognized that cleavage of the referenced carbon-hydrogen bond would have been slow under physiological conditions), 61:24-62:2 ("Itou and…D[oe]ring later on talked about…basically it's an irreversible step"), 73:6-74:4 ("there's another experimental study later by D[oe]ring as well"), 75:5-6 ("I think there were more than one in D[oe]ring, actually, as I recall"). Accordingly, both the nature of the reaction and its position in the pathway made it a prime and favorable location to inhibit lipofuscin formation, as I explained repeatedly before. A priori calculations of the specific rate constants of the various steps in the pathway were not required to reasonably conclude that C_{20}-deuteration would reduce the concentration of activated ([1,5]-shifted) NRPE, the limiting reactant required for the bimolecular condensation reactions that resulted in undesirable lipofuscin pigments A2E and ATR-dimer.

EX1080 (Guengerich Reply Decl.), ¶53.

Pet. Reply, 7-8; PO Sur-Reply, 8.

Literature Precedents Supports Substitution

Trial Confirms: Roth and Itou Support Strong Expected KIE

Extreme conditions required to speed up slow reaction

Q So what is the implication of the forced conditions in the gas phase that were required to force the 1,5 sigmatropic rearrangement to go forward in the Roth reference?

A Well, it's an inherently difficult reaction, and so it takes extreme conditions to make this proceed.

Q And is there similarity or dissimilarity between that and the conditions used in the Doering reference?

A They're very similar in -- well, somewhat different temperatures, but both very high and for long periods of time.

Q And what conclusion, if any, do you draw based on your experience and expertise regarding the impact of C20 deuteration of retinol on the formation of lipofuscin based on the Roth and Doering references?

A Well, it would be expected to be a very slow reaction, which makes some logic because it's -- you know, it -- for many people, it's actually a very slow, lifelong process.

Q Therefore, what impact would you expect to result from C20 deuteration of retinol?

A It should slow down the production of these unwanted molecules by slowing down the reaction.

EX2209 (Guengerich 2nd Depo. Tr.), 143:1-144:4.

Pet. Reply, 11-13; PO Sur-Reply, 5, 8.

Literature Precedents Supports Substitution

Roth and Itou Support Strong Expected KIE

Structural asymmetry ≠ transition state asymmetry

NRPE in the A2E pathway. EX2052 ¶¶295-298. *Roth*'s large KIE is property of the highly symmetric cis-pentadiene hydrocarbon—*Roth*'s reason for selecting cis-pentadiene in the first place. EX1015, 3-4; EX2052 ¶¶296-297. By contrast, NRPE is a large, complex, and highly asymmetric heteromeric molecule with different potential electronic resulting from the involvement of nitrogen in the 1,5 shift. EX2052 ¶298. At best, only a small *intrinsic* effect would be expected for a non-symmetrical transition state. EX1015, 3-5; EX2052 ¶132.

POR, 42-43.

57. Dr. Prestwich opines that the large structure branching out from the 1,3-pentadiene in NRPE rendered Roth irrelevant. EX2052, ¶¶220, 274, 295-299. Dr. Prestwich opines that the "symmetrical structure" of (*Z*)-1,3-pentadiene "was expected to produce a significant KIE due to a highly symmetrical transition state," but that NRPE has "bulky and amphiphilic" arms and a nitrogen that he speculates might "stabilize the transition state differently" or "affect" the KIE. EX2052, ¶¶297-298. Dr. Prestwich's testimony gives the false impression that the transition state symmetry refers to the structural symmetry of the molecule. That is not correct. Dr. Prestwich provides no support for his arguments conflating structural

EX1080 (Guengerich Reply Decl.), ¶57.

Pet. Reply, 11-13.

Literature Precedents Supports Substitution

Roth and Itou Support Strong Expected KIE

Nitrogen does **not** oblate or diminish strong KIE

correct. Dr. Prestwich provides no support for his arguments conflating structural symmetry with symmetrical transition states. Contrary to Dr. Prestwich's unsupported speculation, a POSA would not assume that the transition state of the reaction was asymmetrical. Rather, based on Mata's identification of the NRPE reaction as a [1,5]-sigmatropic rearrangement, a POSA would have recognized that the transition state of the reaction was likely to be symmetrical and subject to a strong KIE as Roth and Itou taught. Dr. Prestwich never testifies that the nitrogen in NRPE would oblate or diminish the strong KIE. It would not. In fact, analogous molecules were well known in the art to be prone to strong KIEs.

EX1080 (Guengerich Reply Decl.), ¶57.

Pet. Reply, 12.

Literature Precedents Supports Substitution

Mowery and Verdegem Support Strong Expected KIE

Mowery and Verdegem required:

- "Non-physiological"
- "Caustic,"
- "combustible,"
- "extreme" alkaline environment to force the reaction.
- *See* slide 58

58. Dr. Prestwich argues that Roth measured the KIE in a gas phase but that NRPE's [1,5]-shift can occur via general acid-base chemistry under aqueous conditions, "as with in vivo systems." EX2052, ¶¶220, 278-281 (citing EX2077, 1; EX2078, 1, 3); see also EX2052, ¶¶289-294 (arguing "13-*cis*-retinylidene-*n*-butylamine easily isomerizes" when non-physiological bases are employed). But these references used non-endogenous, caustic (and even combustible) bases (e.g., sodium hydride) to force a specific base-catalysis reaction. Dr. Prestwich admitted that this does not reflect physiological conditions. EX1070, 159:16-161:13. Nor is it general acid-base catalysis. The fact that Mowery and Verdegem had to introduce non-physiological, strong bases into the system to force the reaction is not dissimilar to the high temperatures (resulting in gas phase reactions) required to drive the [1,5]-sigmatropic rearrangement in Roth and Itou. In each case, extreme conditions were applied because the reaction is so slow under physiological conditions. Accordingly, a POSA would have reasonably expected a strong KIE even under Dr. Prestwich's proposed mechanism.

EX1080 (Guengerich Reply Decl.), ¶58.

Pet. Reply, 11, 12-13.

Literature Precedents Supports Substitution

Mowery and Verdegem Support Strong Expected KIE

Not performed under physiological conditions

Q. You're aware that sodium hydride is combustible?

A. Yes.

EX1070 (Prestwich Depo. Tr.), 159:16-159:18.

Q. You're aware that sodium hydride can ignite in the air spontaneously?

A. It depends how it's packaged, and how you use the reagent that you receive.

EX1070 (Prestwich Depo. Tr.), 160:7-10.

THE WITNESS: I did not see any references that placed sodium hydride in the -- in the broad outer segments.

Q. The same is true for the other segments, correct?

THE WITNESS: That would be true also.

EX1070 (Prestwich Depo. Tr.), 161:6-161:13.

butylamine easily isomerizes" when non-physiological bases are employed). But these references used non-endogenous, caustic (and even combustible) bases (e.g., sodium hydride) to force a specific base-catalysis reaction. Dr. Prestwich admitted that this does not reflect physiological conditions. EX1070, 159:16-161:13. Nor is

EX1080 (Guengerich Reply Decl.), ¶58.

I should point out, while we're on Verdegem, he doesn't use an enzyme. He's actually using a sodium hydride, which is an extremely strong base, as I think I've pointed out. This is actually flammable. You have to be very careful with this and keep it dry. You can't even put it into water.

EX2209 (Guengerich 2nd Depo. Tr.), 115:5-10.

THE WITNESS: Mowery did not use an enzyme. He used a very high concentration of butylamine in the solvent chloroform.

EX2209 (Guengerich 2nd Depo. Tr.), 122:11-13.

Pet. Reply, 11-13; *see also* Slide 58 (neutral outer segment).

Literature Precedents Supports Substitution

Mowery and Verdegem Support Strong Expected KIE

Not performed under physiological conditions

which are "characterized by a neutral pH"). Indeed, Dr. Prestwich testified that sodium hydride is a combustible, insoluble base that does not appear endogenously. EX1070, 159:11-161:13. It can ignite in the presence of water or even air.

EX1080 (Guengerich Reply Decl.), ¶61.

Q And why is it that you have to keep it dry?

A Well, basically -- I know this from personal experience. If you put water in sodium hydride, you'll get fire.

Q And I just want to ask, are those physiological conditions, but in sodium hydride, is that the physiological conditions that exist in the photoreceptor cells in the eye?

A No. Your eyes would burn up.

EX2209 (Guengerich 2nd Depo. Tr.), 132:21-133:7.

Pet. Reply, 11.

PO's Proposed Mechanism Does Not Undermine REOS

Patent Owner's alternative mechanisms still prone to strong KIE

63. The slowness apparent to a chemist of ordinary skill before September 2007 of the [1,5]-shift under physiological conditions—regardless of whether the mechanism disclosed in Mata/Roth/Itou is believed or whether acid-base tautomerization is considered as proposed by Dr. Prestwich—explains Dr. Prestwich's hypothesis that an enzyme might be responsible for the [1,5]-shift resulting in ***ATR-dimer***. But Dr. Prestwich does not explain or justify his assumption that ***A2E*** might be formed via enzyme-mediated acid/base-catalysis of the [1,5]-shift. Fishkin 2005 teaches specifically that the A2-PE intermediate that results in A2E occurs "through a series of random/nonenzyme-mediated reactions." EX1011, 7091.

64. Nor does Dr. Prestwich assert that C_{20}-deuteration would be expected to lack a significant KIE even under his enzyme-catalyst scenario. Though a POSA before 2007 would think it was unlikely an enzyme existed specifically to catalyze the [1,5]-shift, a POSA would expect that enzymes that non-specifically trigger the [1,5]-shift would be very susceptible to the KIE. Dr. Prestwich's enzyme-catalyst-[1,5]-shift hypothesis does not undermine the motivation for C_{20}-deuteration or the reasonable expectation of success.

EX1080 (Guengerich Reply Decl.), ¶¶63-64.

Acid-base tautomerization:
"Very susceptible to the KIE"
"this would actually slow down the process"

Q What impact would C20 deuteration have on downstream formation of lipofuscin if it were resulting from base catalyzed tautomerization?

MR. CHRISTIE: Objection, form.

THE WITNESS: The expected effect would be that this would be -- the deprotonation would be more difficult, so this would actually slow down the process.

BY MR. MILLS:

Q And is that true regardless of whether it's enzyme mediated or not?

A My answer would be the same, yes.

EX2209 (Guengerich 2nd Depo. Tr.), 132:1-12.

Pet. Reply, 11-13; PO Sur-Reply, 7-8.

PO's Proposed Mechanism Does Not Undermine REOS

Patent Owner's alternative mechanisms still prone to strong KIE

Protein-based mechanism "known to be prone to strong KIEs"

Prestwich proposes that the [1,5]-shift occurs via enzymatic catalysis, and created a graphic to illustrate his proposed mechanism. EX2052, ¶¶274 & Figure 12. Notably, however, Dr. Prestwich does not identify any prior art source for his schematic, and he also does not assert that his proposed reaction mechanism would lack a significant KIE. A significant KIE still would have been reasonably expected for Dr. Prestwich's proposed enzymatic deprotonation.

EX1080 (Guengerich Reply Decl.), ¶55.

of acid-base catalysis he proposes for the [1,5]-shift. Indeed, Dr. Prestwich does not assert that chiral-protein-based catalysis weighs against a strong KIE from C_{20}-deuteration. Indeed, enzymes known to perform the type of general acid-base catalysis invoked by Dr. Prestwich (EX2052, ¶95 (FN20)) were known to be prone to strong KIEs. To the extent Dr. Prestwich is correct that a chiral protein-based catalysis was involved in ***ATR-dimer formation***, this does not argue against C_{20}-deuteration to reduce ***A2E formation***. Instead, it provides good reason to expect C_{20}-deuteration to slow ATR-dimer formation as well.

EX1080 (Guengerich Reply Decl.), ¶59.

As I indicated, just having basic proteins around doesn't just start taking protons off of methyl groups and things like that. That's not a very efficient process.

Q Would you characterize Mr. Christie's proposal as something that occurs frequently or something that occurs rarely or some other way?

A Very rarely.

Q And if that were what was happening, what would be the impact of a C20 deuteration to the Vitamin A?

MR. CHRISTIE: Objection to form.

THE WITNESS: It would slow down the removal of the proton.

BY MR. MILLS:

Q What impact, if any, would that have on the downstream formation of lipofuscin?

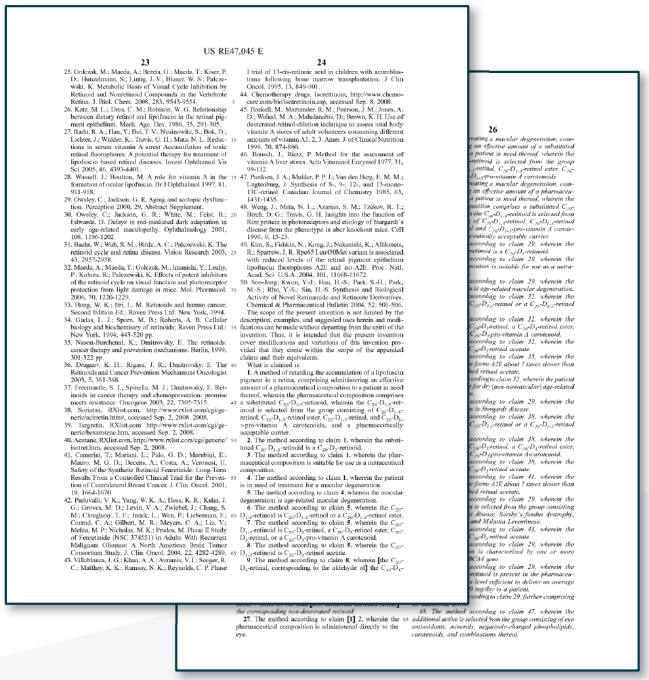
A It should slow it down.

EX2209 (Guengerich 2nd Depo. Tr.), 131:1-18; *id.*, 113:6-13 ("extremely inefficient").

Pet. Reply, 11-13; PO Sur-Reply, 7-9.

Dependent Claims

- Claims 24, 51 (phosphatidyl glycerol)
  - No Dispute: Widder teaches phosphatidylglycerol:
    - benefits MD patients,
    - protects RPE cells from A2E-induced apoptosis.
    - Pet., 60-62; EX1002, ¶¶162-163, 313, 326-333; EX1004, ¶¶69-72, 121-122, 231-233; EX1009, 33:1-7.
- Claims 27, 54 (Direct Administration)
  - No dispute: Widder discloses direct administration to the eye.
  - Local ocular delivery was known to provide essential vitamin A to ocular tissues.
  - Pet., 62-65; EX1002, ¶¶339-46; EX1004, ¶¶57-59, 235-241; EX1009, 25:16-26:40.



EX1001.

Pet., 60-65; Pet. Reply, 26.

WILSON
SONSINI

Secondary Considerations

Patent Owner's Response Arguments

Secondary considerations

- Argues prior AMD and Stargardt treatments failed for lack of efficacy, leaving unmet need
- Argues unexpected success in failed SAGA trial in Geographic Atrophy (AMD)
- Argues unexpected success in TEASE 1 and 3 trials in Stargardt
- Argues skepticism
- Argues praise

POR.

AMD: No failure by others; No Long-Felt, Unmet Need

Prior AMD treatments were successes

FDA-approved medications

- Wet AMD
  - 1. Laser and photodynamic therapy
  - 2. Anti-VEGF treatments
- Dry AMD (GA)
  - 1. Izervay (avacincaptad pegol)
  - 2. Syfovre (pegcetacoplan)

Proof-of concept for effective lipofuscin reduction (but known, unnecessary adverse effects of inhibiting visual cycle)

- Isotretinoin
- Fenretinide
- RPE65 inhibitors

> Q. And GA, geographic atrophy, is a subspecies of age-related macular degeneration; correct?
>
> A. It's -- yes, yes.

EX1069 (Del Priore Depo. Tr.), 232:9-12.

Pet. Reply, 19-23; EX2192, ¶102.

AMD: No failure by others; No Long-Felt, Unmet Need

Prior AMD treatments were successes

FDA approval wet AMD:

- Physicians "proud" to administer
- Dr. Del Priore added an exclamation point trying to "capture the exuberance of physicians"

Q. So you say there, "We are seeing posts on social media with physicians being proud to deliver intravitreal injections of complement inhibitors in patients with geographic atrophy."

Do you see that?

A. I do see that, yes.

Q. And then it says, "Finally, we have a drug to treat non-exudative age-related macular degeneration."

Do you see that?

A. Yes, I do.

Q. And you finished that latter sentence with an exclamation point for emphasis; correct?

A. I finished it with an exclamation point, yes.

Q. And the exclamation point is for emphasis?

A. I'm sorry?

Q. The exclamation point is for emphasis?

A. The exclamation point is to try and capture the exuberance of physicians posting on social media about the new availability of complement inhibitory drugs.

Q. And that refers to the two FDA-approved drugs that we've been discussing today; right?

A. Yes, it does.

EX1069 (Del Priore Depo. Tr.), 251:18-252:18 (quoting EX2171 (Del Priore)).

Pet. Reply, 19.

AMD: No failure by others; No Long-Felt, Unmet Need

Prior AMD treatments were successes

FDA-approval dry AMD (GA)

- 1. Izervay (avacincaptad pegol)
- 2. Syfovre (pegcetacoplan)

atrophy.[1–3] This debate arises from our own success, as 2 complement inhibitory drugs have been recently approved by the U.S. Food and Drug Administration, pegcetacoplan and avacincaptad pegol.[4–6] Monthly intravitreal avacincaptad pegol reduced the mean square-root-transformed geographic atrophy area growth rate by 14% at 1 year (2 mg dose) and by 28.1% (2 mg cohort) and 30.0% (4 mg cohort) at 18 months versus sham.[7–9] Intravitreal pegcetacoplan (15 mg/0.1 mL) monthly or every other month slowed geographic atrophy lesion growth by 21% and 16%, respectively, at 12 months.[10]

EX2171 (Del Priore), 207.

Q. And so I just want to make sure I understand, when you say "our own success," the success is the pegcetacoplan and the avacincaptad pegol drugs that were approved by the FDA for the treatment of geographic atrophy secondary to dry AMD; correct?

A. That is correct, yes.

EX1069 (Del Priore Depo. Tr.), 249:17-23.

Pet. Reply, 19.

AMD: No failure by others; No Long-Felt, Unmet Need

Prior AMD treatments were successes

FDA approval dry AMD:

- "therapeutic" already available to patients
- "much excitement in the field"
- "largest acquisition" of ophthalmic startups

Q. The second sentence says, "With the approval of pegcetacoplan by the FDA for the treatment of geographic atrophy secondary to AMD," and then it continues on to say, "a much needed therapeutic option has become available to patients."

Do you see that?

A. It does say that, yes.

Q. And I just want to make sure I understand when it's talking about a much needed therapeutic option that's become available to patients, it's referring to the pegcetacoplan that was approved by the FDA; correct?

A. Yes.

EX1069 (Del Priore Depo. Tr.), 247:14-248:2 (quoting EX1067).

Q. In that same column, but further down, right before the next paragraph, so the second to the last sentence, it says, "This progress has generated much excitement in the field, as evidenced by the recent acquisition of Iveric Bio by Astellas for the staggering sum of $5.9 billion."

Do you see that?

A. I do.

Q. So what you are referring to as progress that generated much excitement in the field, that's the FDA approval of those two drugs that we've been talking about; correct?

A. Yes.

Q. And that $5.9 billion that you call a staggering sum, why do you call it a staggering sum?

A. It's one of the larger acquisitions of ophthalmic startups. It might be the largest actually, but it's a pretty large acquisition.

EX1069, 249:24-250:18 (quoting EX2172 (Del Priore)).

Pet. Reply, 19-20.

AMD: No failure by others; No Long-Felt, Unmet Need

Prior AMD treatments were successes

FDA approval dry AMD:

- "existing treatments"
- "the only treatments"

Q. Going back to page 207, on the right-hand column, towards the top of the page, starting about six lines down, it says, "Limiting progression of geographic atrophy is an important addition to our treatment armamentarium."

Do you see that?

A. I do see that phrase.

Q. So what is a treatment armamentarium?

A. A treatment armamentarium refers to a potential portfolio of treatments as the field evolves.

Q. So are you saying that the FDA-approved drugs for geographic atrophy are merely potential treatments for geographic atrophy, or are they existing treatments for geographic atrophy?

* * *

A. Can you repeat the question for me?

Q. Are you saying that the FDA-approved treatments for geographic atrophy are merely potential treatments or are they existing treatments?

* * *

A. So at the time this editorial was written, they were existing treatments for geographic atrophy.

Q. And at the time this editorial was written, they were the only treatments for geographic atrophy; correct?

A. Yes. That's correct.

EX1069 (Del Priore Depo. Tr.), 252:19-253:22 (quoting EX2171 (Del Priore)).

Pet. Reply, 19.

No Long-Felt, Unmet Need

For oral administration

No technical difficulty in developing oral AMD treatment;

Patent admits it was routine

Not commensurate with claims

Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); (2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; (3) antioxidants plus zinc; or (4) placebo.

EX1022 (AREDS), Abstract.

Sorsby's fundus dystrophy (SFD) is an autosomal dominant retinal degeneration caused by mutations in the tissue inhibitor of metalloproteinases-3 (*TIMP3*) gene. Mechanisms of the visual loss in SFD, however, remain unknown. In a SFD family with a novel *TIMP3* point mutation, we tested a hypothesis that their night blindness is due to a chronic deprivation of vitamin A at the level of the photoreceptors caused by a thickened membrane barrier between the photoreceptor layer and its blood supply. Vitamin A at 50,000 IU/d was administered orally. Within a week, the night blindness disappeared in patients at early stages of disease. Nutritional night blindness is thus part of the pathophysiology of this genetic disease and vitamin A supplementation can lead to dramatic restoration of photoreceptor function.

EX1041, Abstract.

lipofuscinogenesis.[17] Remofuscin (Katairo, Kusterdingen, Germany) is a compound linked to the reduction of lipofuscin in RPE cells after its oral administration. All mechanisms theoretically decrease

EX2101, 4.

and/or materials. 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, 15:40-45.

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, 16:2-6.

Pet., 43, 45-46, 49; Pet. Reply, 16-18, 23.

No Unexpected PO Success

PO's AMD trial failed

Dr. Del Priore: Calling SAGA a successful trial:

- "That would be problematic, yes."
- Because SAGA "unable to report that they met the prespecified primary endpoint"
- "generally, it's regarded as a failure"

Q. And are you offering an opinion in this case that the SAGA trial results satisfied their prespecified primary endpoint?

A. No, I'm not offering that opinion.

Q. And as far as you're aware, it's correct that the SAGA trial did not meet its prespecified primary endpoint; correct?

A. My recollection of the SAGA trial is they saw in the first cohort of patients a small treatment benefit that was -- may have not been borne out subsequently.

Q. And as a result of that, the SAGA trial was unable to report that they met the prespecified primary endpoint; correct?

A. Yes, that's correct.

EX1069 (Del Priore Depo. Tr.), 267:18-268:7.

Q. What's the implication or the significance of meeting -- failing to meet one's primary endpoint?

A. Well, so if you don't meet your prespecified endpoint, there actually are two possibilities. So the first possibility is the drug doesn't work, which is by far the most likely. And the second possibility, which is very difficult to tease out, is that your study population wasn't large enough. So you might start thinking that if you wind up getting a P value of .06, for example, which means there is a 94 percent chance that the drug really does work, but it's not 95 percent, so it could mean either of those two things. But generally, it's regarded as a failure. Whether or not somebody would want to continue a study with that data is complicated.

Q. Whether somebody wants to continue or not, that's up to them, but if they walked up to you and said, we did not meet our prespecified primary endpoint, but we want you to call it a success, you'd be skeptical of that; right?

* * *

A. That would be problematic, yes.

EX1069 (Del Priore Depo. Tr.), 238:6-239:5.

Pet. Reply, 20.

No Unexpected PO Success

PO relies on preliminary results of two Stargardt trials

TEASE 1 (2021)

Alkeus PHARMACEUTICALS

Source: Alkeus Pharmaceuticals

July 14, 2021 07:00 ET

FDA Grants Alkeus Pharmaceuticals Breakthrough Therapy Designation for ALK-001 (C20-D3-vitamin A) for the Treatment of Stargardt Disease

- Only drug to receive Breakthrough Therapy Designation for Stargardt Disease
- Alkeus Pharmaceuticals to discuss next steps toward filing an NDA with the FDA
- Ongoing clinical trial of ALK-001 in dry age-related macular degeneration

SOMERVILLE, Mass., July 14, 2021 (GLOBE NEWSWIRE) -- Alkeus Pharmaceuticals, Inc., a private, late-stage biopharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation to ALK-001 for the treatment of Stargardt Disease.

ALK-001 (C20-D3-vitamin A) is a chemically-modified form of vitamin A developed to treat multiple retinal degenerative diseases. The investigational treatment is taken as a once-a-day. Clinical data indicates that ALK-001 safely slows the progression of Stargardt while preserving the normal visual cycle. ALK-001 is the only drug to receive Breakthrough Therapy Designation for Stargardt Disease.

Stargardt disease is a progressive inherited retinal degenerative disease that causes irreversible vision loss leading to blindness. An estimated 40 to 60,000 people in the United States have this rare and serious condition. Symptoms typically begin in childhood or adolescence. There is currently no approved therapy for Stargardt disease. Almost everyone diagnosed with the disease will become legally blind.

"Obtaining Breakthrough Therapy Designation is a transformative milestone in Stargardt disease," said Leonide Saad, PhD, CEO of Alkeus Pharmaceuticals. "The results from our Phase 2 trial provide a strong basis for regulatory filing and approval of ALK-001 for the treatment of Stargardt disease. We look forward to working with the FDA and other regulatory agencies so that we can bring ALK-001 to patients as quickly as possible."

The FDA granted ALK-001 Breakthrough Therapy Designation after reviewing data from Alkeus Pharmaceuticals' Phase 2, double-masked, randomized, placebo-controlled trial in Stargardt disease. Data from the trial and other ongoing studies are expected to be reported later in the year. Breakthrough Therapy Designation is a process designed by the FDA to expedite the development and review of promising experimental drugs. Previously, the FDA granted ALK-001 Orphan Drug Designation.

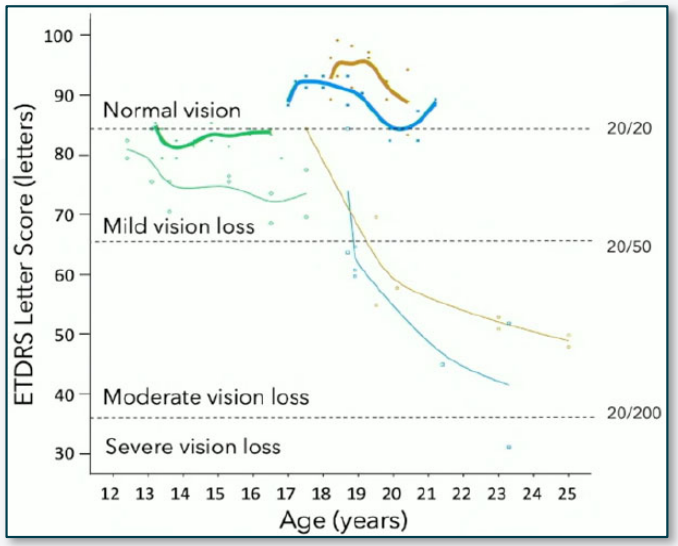
Clinical trials for ALK-001 are also underway for patients with dry age-related macular degeneration (AMD). AMD is the number one cause of unpreventable blindness in the USA. Information about clinical trials and expanded access (compassionate use) can be found on the company's website at www.alkeuspharma.com.

Corporate Contact: Gabrielle DeBartolomeo (pr001@alkeuspharma.com)

The Trustees of Columbia Univ. Ex. 2096 - Page 1 of 1
Gene Company Pty Ltd v. The Trustees of Columbia Univ. - IPR2024-00313

EX2096.

TEASE 3 (ongoing)



EX1087, 19.

POR, 51; Pet. Reply, 21-22.

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Dr. Del Priore:

- Clinical trial should use qualified, fully blinded, and independent readers
- PO conducted "most of its actual science" in-house

Q. What is an independent reading center?

A. So essentially for a very high quality study, you want the photographs to be read at an institution that's not actually treating the patients and never actually sees the patients. The ideal reading center would actually have photographs that are sent to it that are masked. And in a really good study, you wouldn't even know what sequence the pictures were taken in, so that prevents bias basically. It prevents somebody from saying oh, yeah, this drug appears to be working because they know that picture A actually came two years before picture B. So you can mask all that so the reading center personnel don't actually know that.

EX1069 (Del Priore Depo. Tr.), 224:11-25.



EX1079 (Saad Depo. Tr.), 87:14-22.

Pet. Reply, 20-21.

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Dr. Del Priore: readers should not be part of the company sponsoring the trial

- "that would not have been appropriate"

Q. Would it have been appropriate to have an executive at the company sponsoring the trial be arbitrating or adjudicating the reading images instead of using an independent reading center?

* * *

A. In my opinion, that would not have been appropriate.

EX1069 (Del Priore Depo. Tr.), 227:11-18.

Pet. Reply, 20.

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Dr. Del Priore:

- Clinical trial should use qualified, fully blinded, and independent readers
- PO conducted "most of its actual science" in-house



EX1079 (Saad Depo. Tr.), 89:9-13.

> Although Alkeus functions primarily as a lean biotech and outsources many of its activities, most of its actual science is done in-house. After scientific milestones have been achieved,

EX2179, 3.

Q. Okay. And at the time that you hired her in the 2017-2018 time frame, did she have prior experience grading retinal images?

A. I do not believe so.

Q. And at that time -- this is -- maybe sounds like a silly question, but she was not an ophthalmologist. Correct?

A. She's not an ophthalmologist, that I know of.



EX1079 (Saad Depo. Tr.), 91:4-16.

Pet. Reply, 20-21; EX1079, 151:4-13, 181:7- 204:2 (same).

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Dr. Del Priore:

- Clinical trial should use qualified, fully blinded, and independent readers
- PO conducted "most of its actual science" in-house



EX1079 (Saad Depo. Tr.), 89:9-13.

Although Alkeus functions primarily as a lean biotech and outsources many of its activities, most of its actual science is done in-house. After scientific milestones have been achieved,

EX2179, 3.

Q. Prior to your work at Alkeus, had you graded retinal images?

A. No.

Q. Who trained you how to grade retinal images?

A. I worked with Dr. Washington, the cofounder of Alkeus.

Q. Was Dr. Washington involved in the grading of images for the TEASE-1 study?

A. No.

EX1079 (Saad Depo. Tr.), 92:1-10.



EX1079 (Saad Depo. Tr.), 94:3-8.

Pet. Reply, 20-21; EX1079, 151:4-13, 181:7- 204:2 (same).

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Dr. Del Priore:

- Clinical trial should use qualified, fully blinded, and independent readers
- PO conducted "most of its actual science" in-house

Q. And then I'm -- just to clear it out, was Dr. Washington involved in the grading of images for any of the TEASE studies?

A. Not -- he's involved in the scientific part. So not for, let's say, the database grading. Will he be looking at an image, provide some opinions? Yes. Will he be grading in a systematic fashion over time? No.

Q. And that's true for which studies?

A. For all studies.

[redacted]

EX1079 (Saad Depo. Tr.), 92:11-25.

Pet. Reply, 20-21; EX1079, 151:4-13, 181:7- 204:2 (same).

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

In-house "science" using unqualified interns

Q. Do you know who Michael Song is, S-o-n-g?

* * *

A. Michael Song was one of our interns.

* * *

Q. It says "Clinical operations intern at Alkeus Pharmaceuticals Inc., part-time."

Do you see that?

* * *

A. I see that.

Q. And the dates are August 2020 through February 2022. Is that correct?

* * *

A. That's what it says.

EX1079 (Saad Depo. Tr.), 183:4-186:13 (citing EX1074).

Q. The entry under that says "Tufts University Bachelor of Science, BS, Biology, General" between the years of 2019 and 2023.

* * *

A. I see those words written.

Q. When Michael Song was hired at Alkeus, did you know that he was an undergraduate student at Tufts University?

* * *

A. When we hire interns, they are usually students in universities.

EX1079 (Saad Depo. Tr.), 189:7-20.

Q. Okay. The description, the first sentence says, "Aided in the development of novel therapies for dry, age-related macular degeneration, Stargardt disease, and other rare genetic ophthalmic diseases with clinical trials of gildeuretinol (ALK-001)." Correct?

* * *

A. Again, that's what's written in that document.

Q. The next sentence says, "Performed independent data entry and verification, reviewed ocular imagery, prepared narrative literature reviews and briefs, as well as systematically organized TEASE and SAGA study data." Correct?

* * *

A. This is what's written on this.

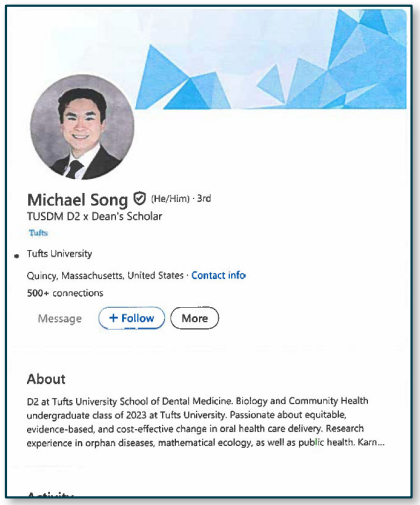
EX1079 (Saad Depo. Tr.), 187:8-25 (citing EX1074).

Pet. Reply, 20-21; EX1074-EX1078 (unqualified interns); EX1079, 151:4-13, 181:7- 204:2.

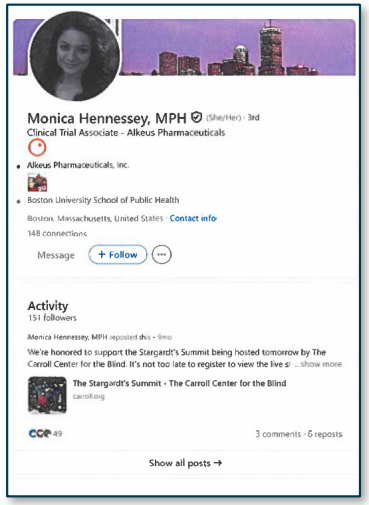
No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

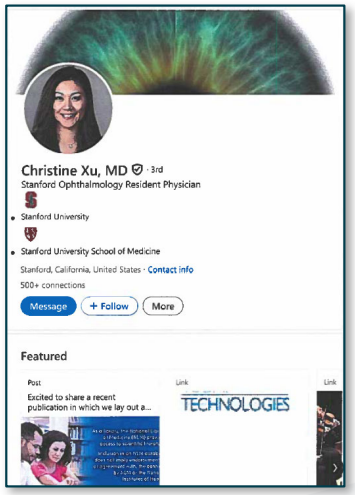
In-house "science" using unqualified interns



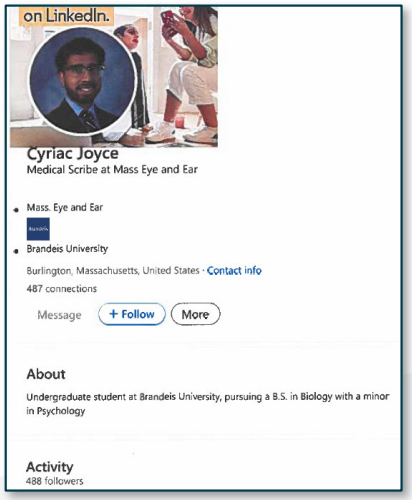
Michael Song
EX1074



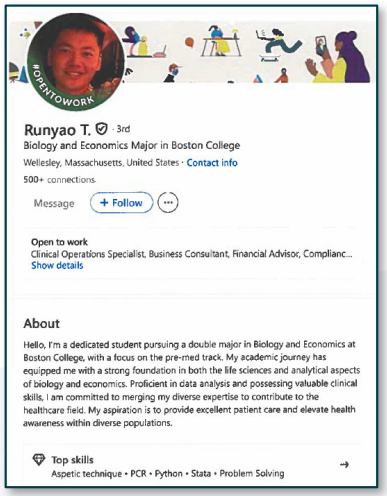
Monica Hennessey
EX1075



Christine Xu
EX1076



Cyriac Joyce
EX1077



Runyao Tong
EX1078

Q. The next sentence says, "Performed independent data entry and verification, reviewed ocular imagery, prepared narrative literature reviews and briefs, as well as systematically organized TEASE and SAGA study data." Correct?

* * *

A. This is what's written on this.

EX1079 (Saad Depo. Tr.), 187:18-25 (citing EX1074).

Q. And all the way at the bottom of the entry, the second-to-last entry, do you see where it says, "Assist the scientists in clinical data collection and analysis"?

* * *

A. I see those words.

EX1079 (Saad Depo. Tr.), 203:3-9 (citing EX1078).

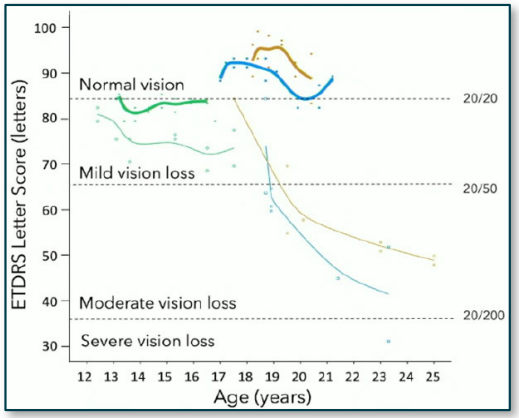
Pet. Reply, 20-21; EX1079, 181:7- 204:2.

No unexpected PO success

PO's preliminary Stargardt trial not performed reliably

Interim Open-Label TEASE 3

- **Apples-to-Oranges**: Participants' ETDRS BCVA compared to older siblings' Snellen acuity measurements.
- Unacceptable to FDA



EX1087, 19.

- Standardized ETDRS BCVA for treated patients
- Snellen acuity for age-matched untreated siblings

P1, Patient 1
Sibling to P1
P2, Patient 2
Sibling to P2
P3, Patient 3
Sibling to P3

Not too different. Visual acuity is inherently variable.

Q. Okay.

A. To give you an example, Snellen visual acuity is what you take at your local optometrist. So if you have glasses and you are satisfied with them, they are acquired using Snellen.

EX1079 (Saad Depo. Tr.), 84:18-24.

in your article here in 2019, you concluded that BCVA may not be a reliable measure to monitor Stargardt 1 progression.

Do you see that?

A. Yes, I do.

EX1069 (Del Priore Depo. Tr.), 260:1-5 (citing EX1068).

Q. And the reference says that BCVA is generally a poor indicator of functional vision in patients with geographic atrophy; correct?

A. It does say that, yes.

Q. And then it says, "The slow rate of visual acuity loss over time precludes BCVA as an adequate primary efficacy endpoint in clinical trials for geographic atrophy."

Do you see that?

A. Yes, I do.

EX1069 (Del Priore Depo. Tr.), 239:21-240:5 (citing EX1066).

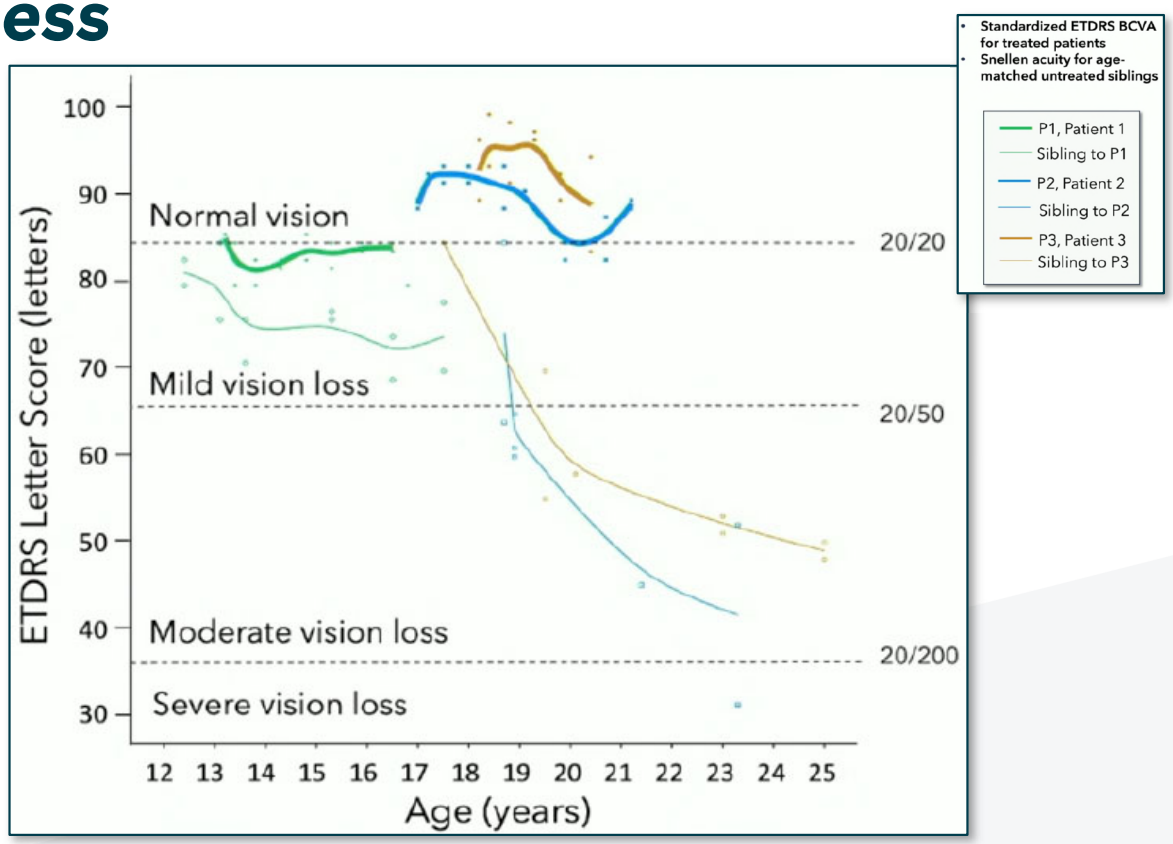
Pet. Reply, 21-22; EX1069, 259:10-17.

No unexpected PO success

PO's preliminary Stargardt trial not performed reliably

Interim Open-Label TEASE 3:

- **Apples-to-Oranges**: Participants' ETDRS BCVA compared to older siblings' Snellen acuity measurements.
- ***At study initiation***, participants had better measurements than siblings at same age.



EX1087, 19.

Cambridge biotech raises $150 million and rehires founder of Vertex

By Jonathan Saltzman Globe Staff, Updated June 5, 2023, 6:00 a.m.



Leonide Saad, cofounder and chief executive of Alkeus Pharmaceuticals,

The median age for when Stargardt patients are considered legally blind is 16 years old, according to Leonide Saad, cofounder and chief executive of Alkeus. "The earlier you have symptoms, the faster you have progression," he added.

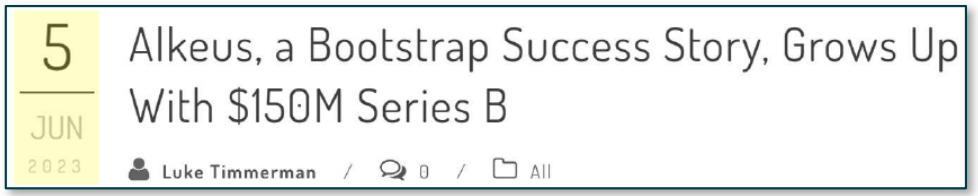
EX1082, 2.

Pet. Reply, 21-22; EX1069, 259:10-17.

No Unexpected PO Success

PO's preliminary Stargardt trial not performed reliably

Preliminary results **lacking** peer review publication.



EX1086, 1.

Research in Vision and Ophthalmology. The data haven't yet been published in a peer-reviewed medical journal, Saad said. Alkeus also isn't yet disclosing the dose – a fact that will have to come out eventually.

EX1086, 2.

Q. And with regard to the TEASE-1 data, you don't recall telling Luke Timmerman that the data haven't yet been published in a peer-reviewed medical journal?

ATTORNEY FELDSTEIN: Objection. Form. Foundation. Beyond the scope of the redirect.

A. I do not remember, no.

EX1079 (Saad Depo. Tr.), 231:3-9.

Pet. Reply, 24.

No Unexpected PO Success

PO's results remain preliminary

Full results still lack peer-review publication
PO's expert confirmed Stargardt need remains unmet
PO never asserted a phase III Stargardt study exists much less has been completed successfully

Alkeus PHARMACEUTICALS

Alkeus Announces $150 Million Series B Financing, Supporting Rapid Registration Path for gildeuretinol (ALK-001) in the Treatment of Stargardt Disease

Vertex Founder and Industry Pioneer Joshua Boger, Ph.D. named as Executive Chairman of Alkeus

June 5, 2023, Cambridge MA – Alkeus Pharmaceuticals announced today that it has raised a

Designation and Orphan Drug Designation to gildeuretinol (ALK-001). Alkeus plans to submit an NDA for approval of gildeuretinol in 2024.

EX2097, 1-2 (June 5, 2023).

possible. Alkeus plans to submit an NDA for approval of gildeuretinol in Stargardt disease in 2024.

EX2108 (Alkeus website) (served September 23, 2024).

2021 — June, 2023 — Sept., 2024 — Now


Alkeus PHARMACEUTICALS

FDA Grants Alkeus Pharmaceuticals Breakthrough Therapy Designation for ALK-001 (C20-D3-vitamin A) for the Treatment of Stargardt Disease

- Only drug to receive Breakthrough Therapy Designation for Stargardt Disease
- Alkeus Pharmaceuticals to discuss next steps toward filing an NDA with the FDA
- Ongoing clinical trial of ALK-001 in dry age-related macular degeneration

The Trustees of Columbia Univ. Ex. 2096 - Page 1 of 1
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July 14, 2021 07:00 ET

EX2096.

POR, 51; Pet. Reply, 21, 22, 25; Sur-reply, 21.

No Unexpected PO Success

Despite patient anecdotes and regulatory assistance designation

PO's expert "Still none are available today."

> 282. Stargardt disease was first described over 100 years ago, and its causative gene was discovered in 1997. EX2110 (Koenekoop 2003) at 1. Nonetheless, there were no treatments to slow the progression of (much less cure) Stargardt disease known as of 2007 and still none are available today. EX2172 (Orphanet 2003) at 1 ("There is currently no treatment available for Stargardt's disease."); EX2173 (Anderson 1995) at 2 ("No therapy alters the progression of this condition."); EX2134 (NEI Stargardt Disease 2024) at 3 ("Doctors haven't found a treatment for Stargardt disease yet."); EX2135 (UCSF Stargardt Disease 2024) at 1 ("Stargardt disease currently has no treatments."); EX2149 (FDA Stargardt Disease 2022) at 6 ("No treatment currently exists, and the disease progresses to legal blindness in almost all patients.").

EX2192 (Del Priore Decl.), ¶282.

Pet. Reply, 21-22; EX2192, ¶¶102, 286.

Clinical Results Not Commensurate with Claims

Clinical study protocol employed at least 14 mg/day, 24 months

- No claim limited to 14 mg/day
- No claim limited to daily oral administration for 24 months
- No claim limited specifically to oral treatment for ABCR-linked Stargardt disease.

EX1079, 131:13-25.

Q. And it says daily oral administration for 24 months?

A. Yes.

Q. Okay. So is that the intervention in all three of the TEASE-1 through the TEASE-3 studies?

* * *

A. That's what's listed in this document.

Q. And is that accurate?

* * *

A. I believe that it is.

EX1079 (Saad Depo. Tr.), 136:16-137:2.

Q. I think you told me before that the dosage is the same. Correct?

ATTORNEY FELDSTEIN: Object to form.

A. Except for the 24 milligrams. The 14 milligrams were the same.

EX1079 (Saad Depo. Tr.), 138:10-14.

Pet. Reply, 18, 22; EX1079, 135:9-139:11.

Clinical Results Not Commensurate with Claims

Clinical study protocol employed secret formulation

Trade secret formulation not disclosed, not claimed

Q. Is that formulation the same formulation that was used in the TEASE-1 study?

A. That's correct. That would be the same formulation.

Q. Is that the same formulation that was used in the TEASE-2 study?

A. Yes. We have only used one formulation from the beginning.

EX1079 (Saad Depo. Tr.), 68:5-12.

Q. Okay. And you said you had some knowledge as to what that formulation is.

Can you go ahead and tell me what it is that you understand the formulation of ALK-001 is?

ATTORNEY FELDSTEIN: I'm going to stop, as the formulation details are beyond the scope. If you want to continue asking that, we're going to have to stop the deposition.

EX1079 (Saad Depo. Tr.), 68:18-25.

ATTORNEY MILLS: So you don't get to stop the deposition. It's not --

ATTORNEY FELDSTEIN: Okay. We'll stop the deposition and we'll contact the board. I'm not going to allow you to delve into his trade secret information.

EX1079 (Saad Depo. Tr.), 69:10-15.

Pet. Reply, 18-19.

Clinical Results Not Commensurate with Claims

Clinical study very narrow patient population

TEASE required Stargardt 1 diagnosis; excluded patients taking vitamin A or beta-carotene

Q. In the second bullet point, do you see that it says, "Has a clinical diagnosis of typical autosomal recesssive Stargardt macular dystrophy (STGD1)"?

A. I do see that.

Q. Is -- and that's Stargardt 1?

A. STGD1 would stand for Stargardt 1.

Q. So that's a particular type of Stargardt?

A. Stargardt 1 is a particular type of Stargardt, yes.

EX1079 (Saad Depo. Tr.), 131:13-22.

Q. So in the TEASE studies, the patients were excluded from the trial if 30 days prior to enrollment they had taken a supplement containing vitamin A or beta-carotene. Is that correct?

A. That's -- it is listed as one of the main exclusion criteria.

EX1079 (Saad Depo. Tr.), 133:22-134:2.

Pet. Reply, 18, 23.

PO's Skepticism Arguments Fail

Dr. Saad incorrectly attributed skepticism to investors he purposefully avoided

Dr. Saad sought to ***avoid*** venture funding.

- Admitted as much in interviews.
- Struggled to recall the interviews in deposition.

In the meantime, Saad ran Alkeus himself. He negotiated deals with manufacturing contractors and physicians at clinical testing sites. He secured grants from the FDA and National Institutes of Health. He said he was reluctant to relinquish control, so he largely stayed away from venture funding.

EX1081, 3.

although I was still on the board, having retired in 2009. He came to me and said, 'Can you help me get this configured to go in the clinic?' And I said, 'That's great. Are you going to start a company?' And he said, 'No, I want to do it myself.' I went, 'O.K., that can be done.'"

EX1084, 2-3.

Around that time, Boger asked Saad if he planned to expand the company. When Saad said he wanted to await clinical results, Boger said, "O.K., nothing more for me to do right now. Get back to me when you have results."

EX1084, 3.

Q. Do you recall giving an interview to the Boston Business Journal?

* * *

A. I do not recall.

Q. Do you recall telling Rowan Walrath at the Boston Business Journal in June 2023 that Mr. Boger left Alkeus Pharmaceuticals because you told him that you wanted to wait to build the company until there were clinical results?

* * *

A. I do not recall.

Q. Do you recall giving an interview to Ben Fiddler at Biopharma Dive on or about June 5, 2023?

* * *

A. I do not recall.

Q. Do you recall telling Mr. Fiddler that you largely stayed away from venture funding for Alkeus Pharmaceuticals because you were reluctant to relinquish control over the company?

* * *

A. I do not remember those words.

EX1079 (Saad Depo. Tr.), 208:10-209:9.

Pet. Reply, 24.

PO's Skepticism Arguments Fail

Not Commensurate with scope of claims

Alleged skepticism of treating ***humans*** without maintaining ***tight dietary control***.

- Claims have no prohibition on dietary control.
- Claims lack "human" limitation.

A has been shown in *Abca4* KO mice to prevent the disease phenotype [117]. The tight dietary control required to achieve these results in mice may not be feasible in humans, but a Phase I clinical trial (NCT02230228) has at least shown oral ingestion of C20-deuterated vitamin A to be safe. A Phase II trial for STGD1 patients is ongoing (NCT02402660) with

EX2180, 14.

ated analogs. It remains to be proven whether pre-clinical efficacy demonstrated in animal models in the context of complete vitamin A replacement with the C20–D_3 analogs can be translated into clinical efficacy in humans maintained on a standard vitamin A and β-carotene sufficient diet. If complete replacement of natural vitamin A with a C20–D_3 analog is required for clinical efficacy, a comprehensive elimination of vitamin A foods (dairy products, eggs, certain fish, *etc.*) may be necessary. Given that vitamin A can be *de novo* synthesized in the RPE from dietary β-carotene [94,96] additional dietary exclusion of β-carotene-rich fruits and vegetables may also be required. Despite the obvious concern regarding the dependence of clinical efficacy on unattainable dietary restrictions, C20–D_3 treatment represents a potentially attractive approach to inhibiting retinal bisretinoid formation as it seems to lack mechanism-based side effects expected of other classes of drugs inhibiting lipofuscin formation, such as direct visual cycle inhibitors.

EX2161, 7.

Q. So when it says, the patient may be a mammal, in the examples, the mice, those were mammals, correct?

A. Yes.

Q. And the rats, those were mammals?

A. Rodents are, in fact, mammals.

EX1070 (Prestwich Depo. Tr.), 64:22-65:5.

Pet. Reply, 23-24; EX1070, 59:22-66:6.