

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re the Application of:  Inventors: Gregory I. Ostrow et al.  Serial No.: 14/726,139  Filing Date: May 29, 2015  Title: <b>OPHTHALMIC COMPOSITION</b>	Group Art Unit: 1621  Confirmation No.: 7389  Examiner: Zohreh A. Fay  Customer No.: 21971  <hr/> <p style="text-align: center;"><u>Certificate of Electronic Filing</u></p> <p>I hereby certify that the attached <b>Response</b> and all marked attachments are being deposited by Electronic Filing on April 5, 2016 by using the EFS – Web patent filing system and addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.</p> <p>By: /Linda Anders/</p>
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Mail Stop Amendment  
Commissioner for Patents  
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**RESPONSE TO NON-FINAL OFFICE ACTION DATED MARCH 7, 2016**

Madam:

This paper responds to the non-final Office Action dated March 7, 2016, setting forth an initial due date of June 7, 2016. Accordingly, this response is timely filed. In the event any additional fee is due, please charge it to Deposit Account No. 23-2415, referencing Docket No. 46682-701.201.

**Listing of the Claims** begins on page 2 of this paper.

**Remarks** begin on page 6 of this paper.

**Conclusion** begins on page 14 of this paper.

### **LISTING OF THE CLAIMS**

This listing of claims will replace all prior versions and listings in the above-referenced patent application. The following amendments are without prejudice and do not constitute an admission regarding the patentability of the amended subject matter and should not so be construed.

1. (Currently Amended) An ophthalmic composition, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
2. (Cancelled).
3. (Cancelled).
4. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.
5. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises one of: at least about 80%, at least about 85%, at least about 90%, at least about 93%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% of the muscarinic antagonist based on initial concentration after extended period of time under storage condition.
6. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition further has a potency of one of: at least 80%, at least 85%, at least 90%, at least 93%, at least 95%, at least 97%, at least 98%, or at least 99% after extended period of time under storage condition.

7. (Original) The ophthalmic composition of claim 1, wherein the extended period of time is one of: about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 8 months, about 10 months, about 12 months, about 18 months, about 24 months, about 36 months, about 4 years, or about 5 years.
8. (Original) The ophthalmic composition of claim 1, wherein the storage condition has a storage temperature of from about 2°C to about 10°C or from about 16°C to about 26°C.
9. (Original) The ophthalmic composition of claim 1, wherein the muscarinic antagonist is present in the composition at a concentration of one of: from about 0.001 wt% to about 0.04 wt%, from about 0.001 wt% to about 0.03 wt%, from about 0.001 wt% to about 0.025 wt%, from about 0.001 wt% to about 0.02 wt%, from about 0.001 wt% to about 0.01 wt%, from about 0.001 wt% to about 0.008 wt%, or from about 0.001 wt% to about 0.005 wt%.
10. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises an osmolarity adjusting agent.
11. (Original) The ophthalmic composition of claim 10, wherein the osmolarity adjusting agent is sodium chloride.
12. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a preservative.
13. (Original) The ophthalmic composition of claim 12, wherein the preservative is selected from benzalkonium chloride, cetrimonium, sodium perborate, stabilized oxychloro complex, SofZia, polyquaternium-1, chlorobutanol, edetate disodium, polyhexamethylene biguanide, or combinations thereof.
14. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a buffer agent.

15. (Original) The ophthalmic composition of claim 14, wherein the buffer agent is selected from borates, borate-polyol complexes, phosphate buffering agents, citrate buffering agents, acetate buffering agents, carbonate buffering agents, organic buffering agents, amino acid buffering agents, or combinations thereof.
16. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition is essentially free of procaine and benactyzine, or pharmaceutically acceptable salts thereof.
17. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition has a dose-to-dose muscarinic antagonist concentration variation of one of: less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%.
18. (Original) The ophthalmic composition of claim 17, wherein the dose-to-dose muscarinic antagonist concentration variation is based on one of: 10 consecutive doses, 8 consecutive doses, 5 consecutive doses, 3 consecutive doses, or 2 consecutive doses.
19. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition further comprises a pD adjusting agent.
20. (Currently Amended) The ophthalmic composition of claim 19, wherein the pD adjusting agent comprises ~~DCl~~ deuterated hydrochloric acid, ~~NaOD~~ deuterated sodium hydroxide, ~~CD<sub>3</sub>COOD~~ deuterated acetic acid, or ~~C<sub>6</sub>D<sub>8</sub>O<sub>7</sub>~~ deuterated citric acid.
21. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition comprises one of: less than 5% of H<sub>2</sub>O, less than 4% of H<sub>2</sub>O, less than 3% of H<sub>2</sub>O, less than 2% of H<sub>2</sub>O, less than 1% of H<sub>2</sub>O, less than 0.5% of H<sub>2</sub>O, less than 0.1% of H<sub>2</sub>O, or 0% of H<sub>2</sub>O.
22. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition is not formulated as an injectable formulation.

23. (Original) The ophthalmic composition of claim 1, wherein the ophthalmic composition is formulated as an ophthalmic solution for the treatment of pre-myopia, myopia, or progression of myopia.
24. (Currently Amended) An ophthalmic solution, comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9, wherein the muscarinic antagonist is atropine, or atropine sulfate.
25. (Original) The ophthalmic solution of claim 24, wherein the ophthalmic solution has a pD of one of: less than about 7.3, less than about 7.2, less than about 7.1, less than about 7, less than about 6.8, less than about 6.5, less than about 6.4, less than about 6.3, less than about 6.2, less than about 6.1, less than about 6, less than about 5.9, less than about 5.8, less than about 5.2, or less than about 4.8 after extended period of time under storage condition.
26. (Cancelled).
27. (Original) The ophthalmic solution of claim 24, wherein the ophthalmic solution comprises one of: less than 5% of H<sub>2</sub>O, less than 4% of H<sub>2</sub>O, less than 3% of H<sub>2</sub>O, less than 2% of H<sub>2</sub>O, less than 1% of H<sub>2</sub>O, less than 0.5% of H<sub>2</sub>O, less than 0.1% of H<sub>2</sub>O, or 0% of H<sub>2</sub>O.
28. (Withdrawn) A method of arresting or preventing myopia development, comprising administering to an eye of an individual in need thereof an effective amount of an ophthalmic composition comprising from about 0.001 wt% to about 0.05 wt% of a muscarinic antagonist and deuterated water, at a pD of from about 4.2 to about 7.9.
29. (Withdrawn) The method of claim 28, wherein the ophthalmic composition is stored at between about 2 °C to about 10 °C prior to first use.
30. (Withdrawn) The method of claim 28, wherein the ophthalmic composition is stored at between about 16 °C to about 26 °C after first use.

### **REMARKS**

This paper is filed in response to the non-final Office Action dated March 7, 2016, and in light of an Examiner Interview conducted on March 30, 2016. In the Office Action, claims 1-27 are rejected as allegedly failing to comply with the written description requirement; claim 20 is rejected as allegedly indefinite; and claims 1-27 are rejected as allegedly obvious over US5,716,952 (“WoldeMussie”) in view of US2012/0015035 (“Widsoet”) and US2012/0203161 (“Herekar”). In addition, all pending claims are rejected under double patenting over co-pending Application No. 14/859,042.

During the Examiner Interview conducted on March 30, 2016, Applicant’s attorney and Examiner Fay discussed potential claim amendments and remarks to overcome the rejections asserted in the Office Action. This response is prepared in furtherance of the discussion. Reconsideration and withdrawal of the rejections are respectfully requested.

### **Written Description**

In the Office Action, claims 1-27 are rejected as allegedly failing to comply with the written description requirement because claim 1 recites “a muscarinic antagonist.” For the sole purpose of expediting prosecution of the present application, independent claims 1 and 24 are amended to recite that the muscarinic antagonist is atropine, or atropine sulfate. As such, the written description rejection should be withdrawn.

### **Indefiniteness**

In the Office Action, claim 20 is rejected as allegedly indefinite for reciting “DCI, NaOD, CD<sub>3</sub>COOD, or C<sub>6</sub>D<sub>8</sub>O<sub>7</sub>.” As amended, claim 20 now recites “deuterated hydrochloric acid, deuterated sodium hydroxide, deuterated acetic acid, or deuterated citric acid.” Accordingly, this rejection should be withdrawn.

### **Obviousness**

To support an obviousness rejection, MPEP §2143.03 requires “all words of a claim to be considered” and MPEP § 2141.02 requires consideration of the “[claimed] invention and prior art

as a whole.” Further, the Board of Patent Appeal and Interferences recently confirmed that a proper, post-KSR obviousness determination still requires the Office make “a searching comparison of the claimed invention – including all its limitations – with the teaching of the prior art.” See, *In re Wada and Murphy*, Appeal 2007-3733, citing *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). In sum, it remains well-settled law that an obviousness rejection requires at least a suggestion of *all* of the claim elements. Applicant submits that the cited references, whether taken alone or in combination, do not teach or suggest D<sub>2</sub>O-based atropine formulations, much less recognizing the technical effects thereof, as discussed in greater detail below.

**WoldeMussie and Widsoet Are Irrelevant to D<sub>2</sub>O-Based Atropine Formulations**

In the Office Action, the Patent Office cites WoldeMussie for allegedly teaching ophthalmic formulations containing a muscarinic antagonist; and Widsoet for allegedly teaching atropine being used as a muscarinic antagonist in ophthalmic formulations (page 6 of the Office Action). Applicant notes that neither reference teaches or suggests D<sub>2</sub>O-based atropine formulations, much less recognizing the technical effects thereof.

**Herekar Cannot Be Properly Modified to Teach D<sub>2</sub>O-Based Atropine Formulations**

The Office Action cites Herekar for allegedly teaching: (1) use of deuterated water in combination with riboflavin in an ophthalmic formulation; (2) increased shelf life of such formulation; and (3) reduced amount of riboflavin if deuterated water is used instead of water (bottom of page 6 of the Office Action). According to the Office Action, one of ordinary in the art would use deuterated water to replace water in WoldeMussie’s ophthalmic formulation to “increase shelf life and to reduce the amount of active ingredient need for the pharmaceutical activity” (top of page 7 of the Office Action).

Applicant disagrees. Applicant first notes that Herekar entire disclosure includes only one sentence that mentions “shelf life.” Specifically, paragraph [0026] of Herekar states that:

Significantly, the riboflavin formulation can also be manufactured with a high concentration of dissolved oxygen. This oxygen enrichment enables the production of greater ROS concentration in a shorter period of time, and, in turn, this makes higher UVA irradiance practical. However, it should be noted that



there may be other means to diffuse oxygen gas into the stroma, which might include, among others, the use of a device that would deliver such oxygen gas to the corneal surface. This oxygen gas then diffuses (albeit slowly) into the stroma, thereby increasing dissolved oxygen. In summary, the ability to increase dissolved oxygen in the stroma enables the use of a higher UVA irradiance exposure to the collagen tissue. This concept of embedding dissolved oxygen in the stroma means that optimum cross-linking (i.e., adequate stiffness of the cornea with minimal side effects) can be achieved in a shorter period of time. **A means to manufacture the enriched oxygen deuterated Rf formulation, that will provide up to and over 1 year of extended shelf life,** is contemplated by this invention. The components of the formulation invention, which are set forth hereinabove, may be optimized for penetration rate, pH, hypotonicity, and lubricity by the proportions that each component is used within the formulation.

This general description of “extended shelf life” appear to be mere wishes as no detailed description or specific example of such “means to manufacture” or “shelf life extension” can be found in Herekar. More importantly, the “contemplated” shelf life extension as described in the cited paragraph is clearly tied to the “means to manufacture”, not to the components of the formulation, much less to deuterated water. Thus, one of ordinary skill in the art would not read Herekar as teaching the use of deuterated water for the purpose of extending shelf life of its riboflavin formulation, much less other ophthalmic formulations such as atropine formulations.

Turning to the Patent Office’s position that Herekar teaches D<sub>2</sub>O-based riboflavin formulations in which the amount of riboflavin can be reduced if deuterated water is used instead of water, Applicant notes that such beneficial effect is specifically tied to the underlying biological mechanism disclosed in Herekar. For example, Herekar’s Abstract and Summary sections both start with the following characterization of Herekar’s invention:

a solution of deuterated water containing a riboflavin-based photosensitizer (Rf aka Vitamin B2) is provided in order to extend lifetimes of UVA/Rf photo-generated intra-stromal singlet oxygen, in combination with UVA delivery profiles of pulsing, fractionation, and optionally auxiliary stromal/Rf hyper-oxygenation in order to accelerate protein cross-linking density rates in ocular tissue.

Later, in the Summary section, Herekar makes it clear that it is the deuterated water in its riboflavin formulation that functions to provide the extended lifetimes of the singlet oxygen. See, e.g. paragraph [0011], stating that:



Lower concentrations of deuterated water with regular water, for example, yields shorter singlet oxygen lifetimes. These lifetimes have approximately a **linear relationship** to the concentration of deuterated water. These lower concentrations are considered acceptable in therapies known or being developed in the art of corneal cross-linking.

As such, one of ordinary skill in the art would understand that the “intended purpose” or “principle of operation” of using deuterated water in Herekar’s riboflavin formulation is such that lifetimes of the singlet oxygen can be extended, which in turn leads to the alleged benefit of requiring less riboflavin because of the singlet oxygen preservation.

With such understanding in mind, Applicant notes that there is insufficient rationale to combine Herekar and other references to produce a D<sub>2</sub>O-based atropine formulation because atropine and its derivatives are recognized “singlet oxygen scavengers”. See, e.g. Abstract of Criado et al. “Scavenging of photogenerated oxidative species by antimuscarinic drugs: atropine and derivatives” Redox Rep 7(6):385-394 (2002), cited in Applicant’s IDS filed on March 29, 2016. In other words, any modification or combination of Herekar and other references to arrive at a D<sub>2</sub>O-based atropine formulation as featured in the amended claims would inevitably frustrate the “intended purpose” or “principle of operation” of Herekar. See MPEP 2143.01 VI (“[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious”). See also, MPEP 2143.01 V (“[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).”

#### **Unexpected Technical Effects of D2O-Based Atropine Formulation**

Finally, Applicant draws the Patent Office’s attention to the surprising data presented in the application. In particular, the formulation with D<sub>2</sub>O yield the following unexpected properties:

- Better stability
- Lower main degradant
- Longer shelf-life

### Better stability

Tables 24A and 24B under paragraph [00329] (Example 11) and Table 15 under paragraph [00300] (Example 9) show atropine sulfate purity data of different formulations. Table 24A shows atropine sulfate formulations in water. Table 24B shows similar atropine sulfate formulations in deuterated water. The pair-wise formulations can be viewed as:

- Formulation 3 and Formulation 7
- Formulation 5 and Formulation 8
- Formulations 10/11 and Formulation 9
- Formulation 13 and Formulation 12

Formulation 8 shows a pD of 6.2 (with effective pH of 5.8; Table 24B). It is formulated similarly as Formulation 5 (Table 24A), with the exception of deuterated water. At week 0, both formulations (5 and 8) contain similar percentage of atropine sulfate (98.16% for Formulation 5 and 98.93% for Formulation 8). However, at week 2, a higher degradation is observed for Formulation 5 across all three temperature ranges while a much lower degradation is observed for Formulation 8. Similarly, at week 4, only 66.83% of atropine sulfate remains at 60 degree C in Formulation 5. In contrast, 92.72% of atropine sulfate remains at 60 degree C in Formulation 8.

Similarly, Formulation 9 shows a higher purity percentage at week 4 across all 3 temperatures than either Formulation 10 or 11. Formulation 12 (pD 7.2; effective pH of 6.8) shows about 46% atropine sulfate at week 4 and 60 degree C while Formulation 13 only retained about 28% atropine sulfate at week 4 and 60 degree C.

Table 24A. Atropine Sulfate Purity as Area-% for H<sub>2</sub>O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
<b>Formulation 3</b> ↓A H <sub>2</sub> O pH 4.8	25/60	98.16	98.16	98.45
	40/75		97.98	97.35
	60 °C		95.94	94.65
<b>Formulation 5</b> ↓C H <sub>2</sub> O pH 5.8	25/60	98.16	97.92	97.54
	40/75		95.88	93.51
	60 °C		80.94	66.83
<b>Formulation 10</b> ↓C H <sub>2</sub> O pH 6.4	25/60	98.66	96.67	95.81
	40/75		91.07	85.27
	60 °C		59.77	42.87

<b>Formulation 11</b> ↓C(2x) H <sub>2</sub> O pH 6.4	25/60	99.47	97.87	96.69
	40/75		90.97	84.26
	60 °C		54.96	34.40
<b>Formulation 13</b> ↓C H <sub>2</sub> O pH 6.8	25/60	97.21	95.42	93.24
	40/75		83.05	73.00
	60 °C		43.99	27.50

Table 24B. Atropine Sulfate Purity as Area-% for D<sub>2</sub>O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
<b>Formulation 7</b> ↓A D <sub>2</sub> O pD 5.2	25/60	98.93	99.07	98.39
	40/75		98.51	97.55
	60 °C		96.70	94.01
<b>Formulation 8</b> ↓C D <sub>2</sub> O pD 6.2	25/60	98.93	98.95	98.51
	40/75		98.53	97.44
	60 °C		95.97	92.72
<b>Formulation 9</b> ↓C D <sub>2</sub> O pD 6.8	25/60	99.29	98.42	98.07
	40/75		95.20	93.22
	60 °C		75.17	65.97
<b>Formulation 12</b> ↓C D <sub>2</sub> O pD 7.2	25/60	98.53	97.17	95.99
	40/75		90.75	84.64
	60 °C		56.78	46.05

### Lower Main Degradant

With respect to the main degradant—tropic acid, Tables 25A and 25B (under paragraph [00330]) further show the percentage of tropic acid are present with each individual formulations. For example, only 4.03% of tropic acid was observed at 60 degree C in Formulation 8 while about 29% of tropic acid was observed at 60 degree C at week 4 in Formulation 5. Formulation 9 contains about 29% of tropic acid at 60 degree C at week 4 while Formulations 10 and 11 each contains about 54% or 62% tropic acid at 60 degree C, respectively. Similarly, Formulation 12 contains about 48% tropic acid at 60 degree C while Formulation 13 contains 69%. As such, the deuterated water stabilizes the atropine sulfate.

Table 25A. Tropic Acid as Area-% for H<sub>2</sub>O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
<b>Formulation 3</b> ↓A H <sub>2</sub> O pH 4.8	25/60	<LOQ	0.12	0.05
	40/75		0.19	0.27
	60 °C		0.90	1.58
<b>Formulation 5</b> ↓C H <sub>2</sub> O pH 5.8	25/60	<LOQ	0.40	0.71
	40/75		2.22	4.35
	60 °C		16.62	29.13
<b>Formulation 10</b>	25/60	0.74	1.90	3.21

↓C H <sub>2</sub> O pH 6.4	40/75		7.61	13.49
	60 °C		37.44	54.06
<b>Formulation 11</b> ↓C(2x) H <sub>2</sub> O pH 6.4	25/60	0.09	1.31	2.64
	40/75		7.61	14.68
	60 °C		42.43	62.23
<b>Formulation 13</b> ↓C H <sub>2</sub> O pH 6.8	25/60	2.21	3.66	6.11
	40/75		15.47	25.80
	60 °C		53.24	69.34

Table 25B. Tropic Acid as Area-% for D<sub>2</sub>O Formulations

Solvent	Condition	t=0	t=2 weeks	t=4 weeks
<b>Formulation 7</b> ↓A D <sub>2</sub> O pD 5.2	25/60	<LOQ	0.07	0.08
	40/75		0.14	0.24
	60 °C		0.71	1.07
<b>Formulation 8</b> ↓C D <sub>2</sub> O pD 6.2	25/60	<LOQ	0.11	0.14
	40/75		0.33	0.65
	60 °C		2.32	4.03
<b>Formulation 9</b> ↓C D <sub>2</sub> O pD 6.8	25/60	0.06	0.55	1.06
	40/75		3.16	6.29
	60 °C		21.09	29.25
<b>Formulation 12</b> ↓C D <sub>2</sub> O pD 7.2	25/60	0.42	1.35	2.62
	40/75		7.27	13.53
	60 °C		38.58	48.15

### Longer Shelf-life

Table 30 under Example 12 (paragraph [00334]) shows the predicted shelf life at temperatures of 40°C, 30°C, 25°C, and 2-8°C for Formulations 2-8 for total Related Substance and for the main degradant tropic acid, respectively. As shown from the table, Formulation 8 has longer shelf life across all 4 temperature ranges when compared with Formulation 5. In particular, at 2-8 degree C, Formulation 8 has a shelf life of about 158 months while Formulation 5 only has a shelf life of about 37 months.

Table 30

Stability Prediction		RS		Tropic Acid	
Formulation	Temperature (°C)	weeks	months	Temperature (°C)	weeks months
<b>2</b>	40	64.5	16.1	40	- -
	30	153.2	38.3	30	- -
	25	241.2	60.3	25	- -
	2-8	1747.9	437.0	2-8	- -
<b>3</b>	40	31.1	7.8	40	99.5 24.9
	30	73.9	18.5	30	268.3 67.1
	25	116.3	29.1	25	451.8 113.0

	2-8	842.9	210.7	2-8	4382.0	1095.5
<b>4</b>	40	30.7	7.7	40	42.1	10.5
	30	73.0	18.2	30	113.7	28.4
	25	114.9	28.7	25	191.5	47.9
	2-8	832.6	208.1	2-8	1857.0	464.2
<b>5</b>	40	5.5	1.4	40	4.9	1.2
	30	13.1	3.3	30	13.2	3.3
	25	20.6	5.2	25	22.2	5.5
	2-8	149.3	37.3	2-8	215.0	53.8
<b>6</b>	40	10.7	2.7	40	8.8	2.2
	30	25.5	6.4	30	23.7	5.9
	25	40.1	10.0	25	39.8	10.0
	2-8	290.5	72.6	2-8	386.5	96.6
<b>7</b>	40	27.9	7.0	40	129.6	32.4
	30	66.4	16.6	30	349.6	87.4
	25	104.5	26.1	25	588.7	147.2
	2-8	757.3	189.3	2-8	5709.4	1427.4
<b>8</b>	40	23.3	5.8	40	33.6	8.4
	30	55.3	13.8	30	90.6	22.6
	25	87.2	21.8	25	152.5	38.1
	2-8	631.6	157.9	2-8	1479.2	369.8

For reasons stated above, the cited references do not teach or suggest the use of deuterated water in an atropine ophthalmic formulation, much less recognizing the technical effect thereof, as summarized above. Accordingly, the obviousness rejections should be withdrawn.

### **Double Patenting**

Turning to the double patenting rejections, all pending claims are over the claims of co-pending Application No. 14/859,042. Applicant requests the Office to hold this rejection in abeyance until an allowable set of claims has been indicated for the present application.

**CONCLUSION**

Applicants submit that this response fully addresses the Office Action dated March 7, 2016 and respectfully request consideration and allowance of the claims.

Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2339. If additional fees are believed to be required, the Commissioner is authorized to charge any additional fees to Deposit Account No. 23-2415 (Attorney Docket No. 46682-701.201).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI  
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Date: April 5, 2016

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