

UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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AQUESTIVE THERAPEUTICS, INC.

Petitioner

v.

IONO PHARMA, LLC

Patent Owner

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IPR2025-00874

U.S. Patent No. 11,021,437 B2

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**PETITION FOR *INTER PARTES* REVIEW**

**UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.1 *ET SEQ.***

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**EXHIBIT LIST**

| <b><u>EXHIBIT NO.</u></b> | <b><u>EXHIBIT DESCRIPTION</u></b>                                                                                                                                                                                                                                                |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1001                      | U.S. Patent No. 11,021,437 B2, entitled “Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine Or A Pro - Drug Thereof”, filed as application serial number 16/347,625 on November 9, 2017, Almoazen inventor, issued on June 1, 2021 (“the ‘437 Patent”). |
| 1002                      | U.S. Patent No. 3,809,714, entitled “Novel Ester Of [(Methylamino)Methyl] Benzyl Alcohol”, Hussain and Truelove inventors, issued on May 7, 1974 (“the ‘714 Patent” or “Truelove 1”).                                                                                            |
| 1003                      | Ashraf M and Sayeed VA, “Considerations in Developing Sublingual Tablets – An Overview,” <i>Pharmaceutical Technology</i> <b>38</b> (11) 2014 (“Asraf”).                                                                                                                         |
| 1004                      | U.S. Patent No. 4,136,145, entitled “Medicament Carriers In The Form Of Film Having Active Substance Incorporated Therein”, Fuchs and Hilmann inventors, issued January 23, 1979 (“the ‘145 Patent” or “Fuchs”).                                                                 |

- 1005           The Almoazen ‘437 Patent application prosecution history file for the ‘437 Patent, serial no. 16/347,625 (“the ‘437 FH” or “Almoazen File History”).
- 1006           U.S. Patent No. 3,825,583, entitled “Ester Of 3-Hydroxy- $\alpha$ -[(Methylamino) Methyl]Benzyl Alcohol”, Hussain and Truelove inventors, issued on July 23, 1974 (“the ‘583 Patent” or “Truelove 2”).
- 1007           Hussain A and Truelove JE: “Prodrug Approaches to Enhancement of Physicochemical Properties of Drugs IV: Novel Epinephrine Prodrug”, Journal of Pharmaceutical Sciences 65(10), 1976 (“Truelove Article” or “Truelove 4”).
- 1008           U.S. Patent No. 3,868,461, entitled “Ester Of 3,4-Dihydroxy-Alpha (Isopropylamino) Methyl Benzyl Alcohol Composition And Anti-Asthma Use Thereof”, Hussain and Truelove inventors, issued on February 25, 1975 (“the ‘461 Patent” or “Truelove 3”).
- 1009           *The Merck Index*, 12<sup>th</sup> Ed., 1996, p. 613.
- 1010           Reserved.

- 1011 USP certificate for epinephrine, dated 14 Aug 2017.
- 1012 The prescription information for the epinephrine used in the EpiPen.
- 1013 The Almoazen '437 Patent Provisional Application for Patent, serial no. 62,421,316, filed on November 13, 2016, Hassan Almoazen ("Almoazen Provisional Application").
- 1014 WO2018/089570 A1 (PCT/US2017/060761), entitled "Pharmaceutical Formulation For Sublingual Or Buccal Delivery Of Epinephrine", Almoazen and Haynes, co-inventors ("Almoazen PCT Application").
- 1015 Florence AT and Attwood D, "Physicochemical Principles of Pharmacy", Fifth edition, Eds. Pharmaceutical Press (2011) ("Florence").
- 1016 U.S. Patent No. 4,145,441, entitled "Sympathomimetic Amines Exhibiting Anti-Hemorrhoidal Activity", Bodor inventor, issued March 20, 1979 ("the '441 Patent" or "Bodor").
- 1017 U.S. Patent Application Publication No. US 2007/0202163 A1, entitled "Fast-Disintegrating Epinephrine Tablets For Buccal

Or Sublingual Administration”, Rawas-Qalaji, *et al.*, inventors, published on August 30, 2007 (“Rawas-Qalaji”).

- 1018 Ettmayer *et al.*, “Lessons Learned from Marketed and Investigational Prodrugs”. *Journal of Medicinal Chemistry* 47(10), 2393-2404, 2004 (“Ettmayer”).
- 1019 Rautio *et al.*, “Prodrugs: design and clinical applications”. *Nature Reviews Drug Discovery* 7, 255-270, 2008 (“Rautio”).
- 1020 Silverman RB., Chapter 8, “Prodrugs and drug delivery systems” in *The Organic Chemistry of Drug Design and Drug Action*. Academic Press, Inc. 1992 (“Silverman”).
- 1021 U.S. Patent No. 11,191,737 B2, entitled “Enhanced Delivery Epinephrine Compositions”, Schobel, *et al.* inventors, claiming benefit of provisional application No. 62/331,996, filed on May 5, 2016 (“Schobel”).
- 1022 Alaadin Alayoubi, Lindsay Haynes, Hemlata Patil, Baher Daihom, Richard Helms & Hassan Almoazen (2016): “Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for

pediatrics”, Pharmaceutical Development and Technology,  
Early Online: 1-5, Published online 6 January 2016 (“Almoazen  
Paper”).

- 1023 Baldessarini, *et al.*, “Hydrolysis of diester prodrugs of  
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1756. Pergamon Press. 1977 (“Baldessarini”).
- 1024 Kristoffersson, *et al.*, “Drug latention of terbutaline”, Acta  
Pharm. Suecica 11, 427-438 (1974) (“Kristoffersson”).
- 1025 Christrup, *et al.*, “Improvement of buccal delivery of morphine  
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165 (“Christrup”).
- 1026-1028 Reserved.
- 1029 Lieberman, *et al.*, “The diagnosis and management of  
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Immunol Sept. 2010 126(3):477-80.e1-42 (“Lieberman”).
- 1030 Hansen, *et al.*, “Ketobemidone prodrugs for buccal delivery”,  
Acta Pharm Nord, 3 (1991) 77-82 (“Hansen 1991”).

- 1031            den Daas, et al., “Improvement of the oral bioavailability of the selective dopamine agonist N-0437 in rats: the in vitro and in vivo activity of eight ester prodrugs”, Naunyn Schmiedeberg’s Arch Pharmacol (1990) 341:186-91 (“den Daas”).
- 1032            Hansen, *et al.*, “Ketobemidone prodrugs for buccal delivery: Prediction of the extent of saliva-catalyzed hydrolysis of various ester prodrugs under simulated in vivo condition”, Int J Pharma, 88, 1992, pp. 229-235 (“Hansen 1992”).
- 1033            A copy of the ‘437 Patent (Exhibit 1001) showing where material from the Almoazen Paper (Exhibit 1022) appears in highlighting.
- 1034            Roche, “Design of biopharmaceutical properties through prodrugs and analogs”, American Pharmaceut. Assoc., Washington, DC, 1977 (“Roche”).
- 1035            A copy of the Almoazen Paper (Exhibit 1022) highlighted to show where material from the Paper appears in the ‘437 Patent (Exhibit 1001).

- 1036 Morrison and Boyd, “Organic Chemistry”. 2<sup>nd</sup> Edition, Chapter Sections 18.1-18-4 (1970) (“Morrison and Boyd”).
- 1037 Streitwieser, et. al, “Introduction to Organic Chemistry”, 4<sup>th</sup> Edition, excerpts (1992) (“Streitweiser”).
- 1038 Reserved.
- 1039 Stepensky, *et al.*, “Long-Term Stability Study of L-Adrenaline Injections: Kinetics of Sulfonation and Racemization Pathways of Drug Degradation”, J Pharm Sci 93:969–980 (2004) (“Stepensky”).
- 1040 Huttunen, K., Raunio, H., Rautio, J., “Prodrugs—from Serendipity to Rational Design”, *Pharmacol Rev* 63:750–771 (2011) (“Rautio II”).
- 1041 Senel & Hincal, “*Drug permeation enhancement via buccal route: possibilities and limitations*”, J Contr Rel 72: 133-144, 2001 (“Senel”).
- 1042-1043 Reserved.

- 1044 Kohn, et. al, “Clinical Comparison of Dipivalyl Epinephrine and Epinephrine in The Treatment Of Glaucoma”, American Journal of Ophthalmology 87:196-201, 1979 (“Kohn”).
- 1045 Reserved.
- 1046 Journal of Medicinal Chemistry, “Manuscript Submission Requirements Checklist”, [https://researcher-resources.acs.org/publish/author\\_guidelines?coden=jmcmr#manuscript\\_submission\\_requirements\\_checklist](https://researcher-resources.acs.org/publish/author_guidelines?coden=jmcmr#manuscript_submission_requirements_checklist), October 29, 2024 (“JMC Manuscript Requirements”).
- 1047-1049 Reserved.
- 1050 Declaration of Jarkko Rautio, Ph.D.
- 1051 Declaration of Nicholas A. Meanwell, Ph.D.

**I. THE PETITION**

Real party-in-interest, Aquestive Therapeutics, Inc. (“Petitioner”), petitions the Patent Trial and Appeal Board (“PTAB”) pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.1 *et seq.*, to institute an *inter partes* review and find unpatentable and cancel claims 1-3 (“the challenged claims”) of U.S. Patent No. 11,021,437 B2, entitled “Pharmaceutical Formulation For Sublingual or Buccal Delivery of Epinephrine or a Pro-Drug Thereof” and assigned to Iona Pharma, LLC (“the ‘437 patent”). There is a reasonable likelihood that Petitioner will prevail with respect to at least one challenged claim in this Petition.

**II. MANDATORY NOTICES (37 C.F.R. § 42.8)****A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))**

Petitioner, Aquestive Therapeutics, Inc., 30 Technology Drive, Warren, New Jersey 07059, is the sole real party-in-interest.

**B. Related Matters (37 C.F.R. § 42.8(b)(2))**

Petitioner has not previously challenged the ‘437 patent and is unaware of any other proceedings involving the ‘437 patent.

**C. Counsel (37 C.F.R. §§ 42.8(b)(3) and 42.10(a))**

Petitioner designates the following individuals as its lead counsel and back-up lead counsel:

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**D. Service Information (37 C.F.R. § 42.8(b)(4))**

Service on Petitioner may be made electronically by using all the following four e-mail addresses together in providing service: [dscola@hbiplaw.com](mailto:dscola@hbiplaw.com); [mchakansky@hbiplaw.com](mailto:mchakansky@hbiplaw.com); [jtgdoCKET@hbiplaw.com](mailto:jtgdoCKET@hbiplaw.com); and [437IPR@hbiplaw.com](mailto:437IPR@hbiplaw.com). Service on Petitioner may be made by Postal Mailing or Hand-Delivery addressed to Lead and Back-up Counsel at the address on the following page, but electronic service to the email addresses above is requested:

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### **III. PAYMENT OF FEES**

Pursuant to 37 C.F.R. §§ 42.103 and 42.15(a), the undersigned authorizes PTO to charge the \$51,875.00 fee for the 3 claims requested for review (request fee of \$23,750.00 and post-institution fee of \$28,125.00) for this IPR Petition to Hoffmann & Baron, LLP Deposit Account No. 08-2461. The undersigned further authorizes payment from and to the above referenced Deposit Account for any additional fees or refund that may be due in connection with this Petition.

### **IV. ADDITIONAL REQUIREMENTS FOR *INTER PARTES* REVIEW**

#### **A. Grounds For Standing (37 C.F.R. § 42.104(a))**

Petitioner certifies that the '437 patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting an IPR challenging claims 1-3 of the '437 patent on Grounds 1-3 detailed below.

#### **B. Identification of Challenge and Relief Requested (37 C.F.R. § 42.104(b) and 37 C.F.R. § 42.22(a)(1))**

The precise relief requested by Petitioner is that claims 1-3 are found unpatentable and cancelled from the '437 patent.

#### **1. Claims for Which IPR is Requested (37 C.F.R. § 42.104(b)(1))**

Petitioner requests inter partes review of claims 1-3 of the '437 patent.

**2. Specific Statutory Grounds on Which the Challenge is Based (37 C.F.R. § 42.104(b)(2))**

| <b>Ground</b> | <b>References</b>                                                                                                                                     | <b>Basis</b>    | <b>Claims Challenged</b> |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------------------------|
| 1             | Truelove 1 (EX1002), Ashraf (EX1003),<br>Almoazen Paper (EX1022)                                                                                      | 35 U.S.C. § 103 | 1-3                      |
| 2             | Truelove 3 (EX1008), Ashraf (EX1003),<br>Almoazen Paper (EX1022)                                                                                      | 35 U.S.C. § 103 | 1-3                      |
| 3             | Trulove 1 (EX1002),<br>Truelove 3 (EX1008), Ashraf (EX1003),<br>Almoazen Paper (EX1022),<br>Fuchs (EX1004),<br>Schobel (EX1021),<br>Florence (EX1015) | 35 U.S.C. § 103 | 1-3                      |

In support of its unpatentability arguments, Petitioner relies on the Declarations of Jarkko Rautio, Ph.D. (“Rautio (EX1050)”) and Nicholas A. Meanwell, Ph.D. (“Meanwell (EX1051)”).

**C. Prior Art References with relevant dates**

Other than Schobel, all references Petitioner relies on issued or were published more than one year before the earliest possible effective filing date of the challenged claims (*i.e.*, November 9, 2017), and are prior art under 35 U.S.C. § 102(a)(1). Schobel, claiming priority to its provisional patent application filed

May 5, 2016, qualifies as prior art under 35 U.S.C. § 102(a)(2) and 35 U.S.C.

§ 100(i)(1)(B).

| <b>35 U.S.C. § 102(a)(1) References</b> | <b>Exhibit</b> | <b>Publication Date</b> |
|-----------------------------------------|----------------|-------------------------|
| Truelove 1                              | EX1002         | May 7, 1974             |
| Ashraf                                  | EX1003         | November 2014           |
| Almoazen Paper                          | EX1022         | January 6, 2016         |
| Truelove 3                              | EX1008         | February 25, 1975       |
| Fuchs                                   | EX1004         | January 23, 1979        |
| Florence                                | EX1015         | 2011                    |

| <b>35 U.S.C. § 102(a)(2) &amp;<br/>35 U.S.C. § 102(d)<br/>35 U.S.C. § 100(i)(1)(B)<br/>Reference</b> | <b>Exhibit</b> |                                             |
|------------------------------------------------------------------------------------------------------|----------------|---------------------------------------------|
| Schobel                                                                                              | EX1021         | <b>Filing Date</b><br>May 4, 2017           |
| Schobel                                                                                              | EX1021         | <b>Effective Filing Date</b><br>May 5, 2016 |

## **V. THE ‘437 PATENT**

The ‘437 patent is directed to sublingual or buccal administration of epinephrine with exhibiting half-life  $t_{1/2}$  values of 1-6 minutes using a rapidly dissolving film. *See, e.g.*, Meanwell (EX1051), ¶¶31, 34, *see also generally* ¶¶29-38; Rautio (EX1050), ¶¶50-52, *see also generally* ¶¶48-69.

### A. Technical Background

Epinephrine (*i.e.*, 3-4-dihydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol), also known as adrenaline, is used to treat various conditions, including anaphylaxis and asthma. *See* Meanwell (EX1051), ¶¶48-50; Rautio (EX1050), ¶45; EX1012, p.1. Due to its low lipophilicity, epinephrine is poorly absorbed through biological membranes, such as the eye and oral mucosa.<sup>1</sup> EX1007, p.1510; Rautio (EX1050), ¶¶40-45.

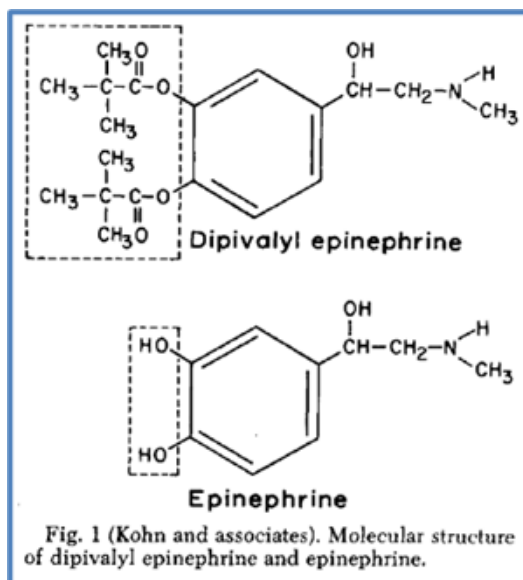
The term “prodrug” describes compounds that undergo chemical transformation within the body to release a parent drug. EX1050, ¶¶36, 38-40, 289-290. For example, a compound may be chemically modified by attaching a “promoiety” to create a new compound (*i.e.*, “prodrug”) to address pharmaceutical, pharmacokinetic, or pharmacodynamic barriers including, *inter alia*, poor lipophilicity, or inadequate permeability through biological membranes. EX1050, ¶¶35-47. Typically, a parent drug (*e.g.*, epinephrine) and promoiety (*e.g.*, ester) are covalently attached to form a prodrug. EX1050, ¶¶30, 37, 45, 292-293. For

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<sup>1</sup> The oral mucosa includes the sublingual and buccal areas of the mouth.

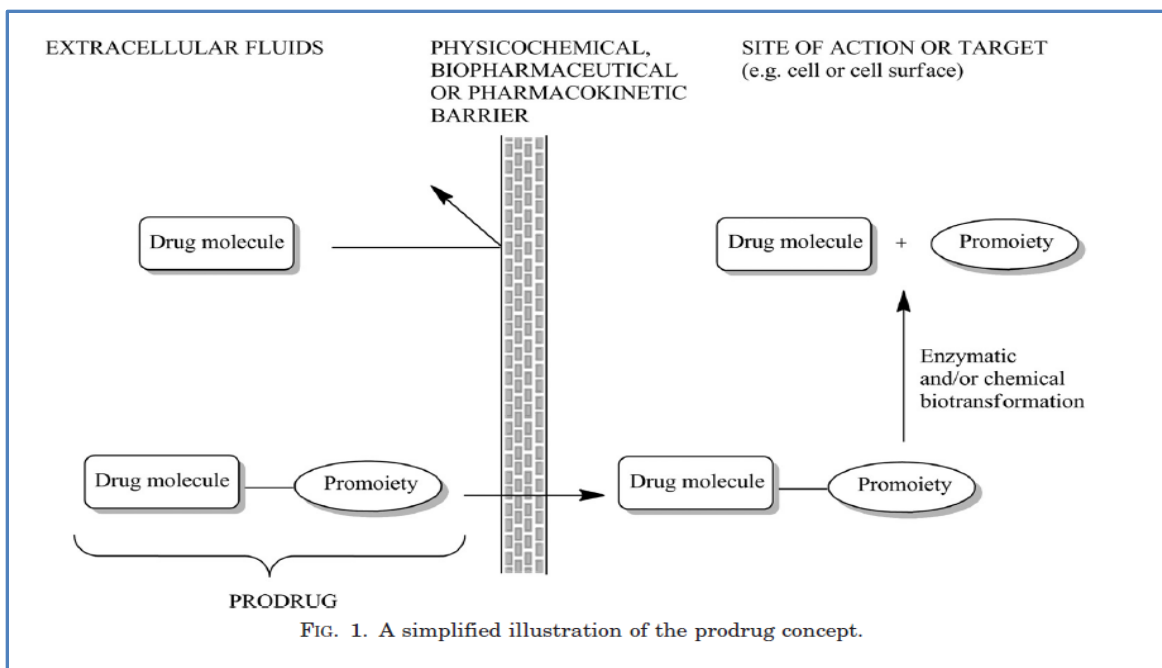
Sublingual and buccal administration refers to placement under the tongue and inside the cheeks. Rautio (EX1050), ¶¶43, 41; EX1015, Figure 9.15, p.364.

example, dipivalyl epinephrine may be formed by the addition of two pivalyl groups to epinephrine:



Kohn (EX1044), p.196. Upon administration of the prodrug, the parent drug (*e.g.*, epinephrine) and promoiety (*e.g.*, ester) are cleaved or broken apart via chemical or enzymatic means to release the parent drug. Rautio (EX1050), ¶¶31, 36, 38-39, 47.

The prodrug concept and the relationship between a prodrug and its promoiety is illustrated below:



EX1050, ¶39; EX1040, p.751.

Prior to the earliest effective filing date of the challenged claims, it was known that the hydroxyl groups on the epinephrine benzene ring could be modified with alkyl ester promoieties to form epinephrine prodrugs with enhanced lipophilicity. *See generally* Truelove 1 (EX1002); Kohn (EX1044), p.196.

## B. The ‘437 Patent: Overview

The ‘437 patent recites diester epinephrine compounds with half-lives  $t_{1/2}$  of 1-6 minutes administered sublingually or buccally via rapidly dissolving films. The ‘437 patent concedes Truelove 1 “synthesized four different prodrugs . . . (see structures 7A, 7B, 7C, 7D),” which are “compounds of the invention.” EX1001,

2:11-12; 6:42-7:9; *see id.*, 4:8-10 (“FIG. 7 shows Anwar A. Hussain and James E. Truelove [Truelove 1] compounds.”).<sup>2</sup> Rautio (EX1050), ¶¶54, 56-60; Meanwell (EX1051), ¶¶34-37. However, the compounds disclosed in Truelove 1 were incorrectly identified as ketone derivatives of epinephrine which a person of ordinary skill in the art (“POSA”) would have recognized could not function as prodrugs because of their inability to metabolize into epinephrine in human plasma and, therefore, would not have a half-life  $t_{1/2}$  that results in the formation of epinephrine. *Infra* pp.26-34.

The ‘437 patent recognizes Truelove 1’s obvious nomenclature errors and provides correct names and structures of Truelove1’s diester epinephrine compounds. *See, e.g.*, EX1001, Figures 5G”, 7A-7D; 6:31-32; 6:42-52. For example, Figure 7 of the ‘437 patent provides the skeletal structures of the diester epinephrine compounds disclosed in Truelove 1:

Now referring to FIG. 7, the compounds of the  
invention as shown in U.S. Pat. Nos. 3,809,714

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<sup>2</sup> The ‘437 patent’s provisional application states that Figure 7 “show[s] exemplary compounds of the present invention”. EX1013, ¶00017; *see* Rautio (EX1050), ¶96.

[EX1002] and US patent 3,825,583 [EX1006] hereby incorporated by reference. Representative molecules include:

**7A** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate<sup>[3]</sup>. . . .

**7B** 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)<sup>[4]</sup>. . . .

**7C** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate<sup>[5]</sup>. . . .

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<sup>3</sup> This compound corresponds to the structure recited in claim 2 where both R substituents of the ester promoieties are CH<sub>3</sub> and is named in claim 3. Meanwell (EX1051), ¶36, n.5; Rautio (EX1050), ¶59, n.11, 178-179.

<sup>4</sup> This compound corresponds to the structure where both R substituents of the ester promoieties are CH(CH<sub>3</sub>)<sub>2</sub>. Meanwell (EX1051), ¶36, n.6; Rautio (EX1050), ¶¶59, n.12, 178-179.

<sup>5</sup> This compound corresponds to the structure recited in claim 2 where both R substituents of the ester promoieties are CH<sub>2</sub>CH<sub>3</sub>, and is named in claim 3 using equivalent nomenclature (*i.e.*, 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropanoate). Meanwell (EX1051), ¶¶36, n.7, 38, n.10; Rautio (EX1050), ¶¶59, n.13, 179-180.

**7D** 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene  
bis(2,2-dimethylpropanoate)[<sup>6</sup>]. . . .

EX1001, 6:42-52 (formatting changed for clarity); Figures 5G”, 7A-D; 6:38-53; 6:57-7:10; Meanwell (EX1051), ¶¶34-37. Additionally, Figure 5G” provides the skeletal structure and the correct name of a diester epinephrine compound disclosed in Tables 1-2 of Truelove 1.<sup>7</sup> *Id.*, ¶38, n.9; Rautio (EX1050), ¶¶176-179; *infra* pp.13, 27-32.

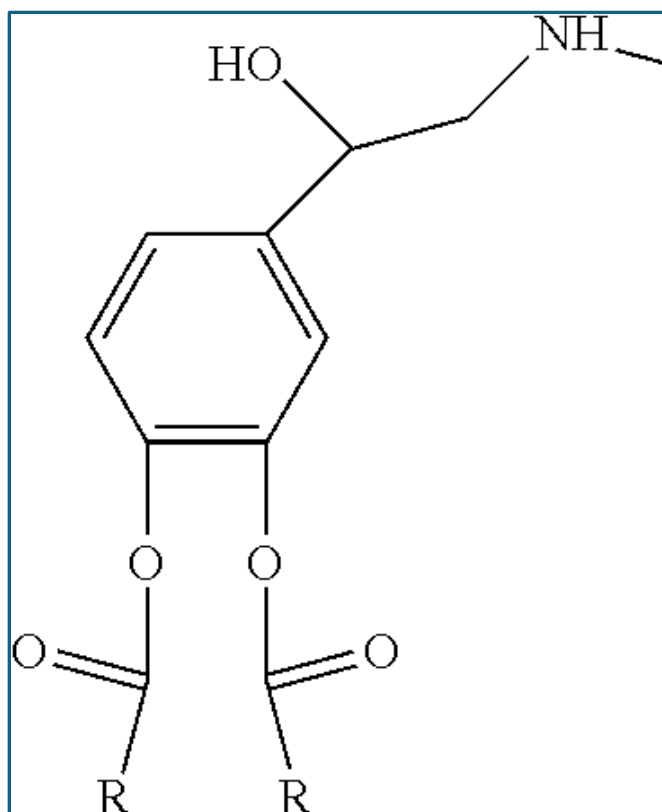
The ‘437 patent confirms that Truelove 1’s nomenclature mistakes would have been obvious to a POSA who would have ignored those errors and, in their place, substituted the correct names of the diester epinephrine compounds disclosed in Truelove 1. *See, e.g.*, Rautio (EX1050), ¶¶128-134, 140-150, 170-179; Meanwell (EX1051), ¶¶64-76, 80-81.

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<sup>6</sup> This compound corresponds to the structure recited in claim 2 where both R substituents of the ester promoieties are C(CH<sub>3</sub>)<sub>3</sub>. Meanwell (EX1051), ¶¶35, n.8, 38, n.12; Rautio (EX1050), ¶¶59, n.14, 178-179.

<sup>7</sup> This compound corresponds to the structure recited in claim 1 where both R substituents of the ester promoieties are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. Meanwell (EX1051), ¶38, n.9; Rautio (EX1050), ¶¶175-179.

The claims 1-2 of the '437 patent refer to the R substituents appearing in the structure shown below as recited in claims 1-2.



### 1. Chart 1

Chart 1 below illustrates that multiple acceptable naming conventions existed to identify the epinephrine diester compounds depicted and named in Figures 7A-7D and 5G” of the ‘437 patent.

| <b>CHART 1</b>            |                                                 |                                                                                                                                                                |                                                                    |
|---------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>'437 Patent Figure</b> | <b>Ester Moiety R Substituent</b>               | <b>'437 Patent Name</b>                                                                                                                                        | <b>Equivalent Name</b>                                             |
| 7A                        | CH <sub>3</sub>                                 | 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate                                                                                                     | 3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol      |
| 7B                        | CH(CH <sub>3</sub> ) <sub>2</sub>               | 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)                                                                                        | 3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol     |
| 7C                        | CH <sub>2</sub> CH <sub>3</sub>                 | 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropanoate<br><br><b>ALTERNATIVELY</b><br><br>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate | 3,4-dipropionyloxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol |
| 7D                        | C(CH <sub>3</sub> ) <sub>3</sub>                | 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2,2-dimethylpropanoate)                                                                                   | 3,4-dipivaloyloxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol  |
| 5G''                      | (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> | 4-(1-hydroxy-2-methylamino)ethyl)-1,2-phenylene dibutyrate)                                                                                                    | 3,4-diisobutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol  |

Rautio (EX1050), ¶¶178-179; Meanwell (EX1051), ¶¶80-81; *infra* pp.26-41.

**C. Earliest Effective Filing Date Is No Earlier Than November 9, 2017**

The '437 patent is a national stage application of PCT/US2017/060761 (EX1014)<sup>8</sup> filed on November 9, 2017 and claiming priority to a provisional application (EX1013) filed November 13, 2016.

Although challenged claims 1-3 recite diester epinephrine compounds having a “half-life  $t_{1/2}$  range from 1-6 minutes,” there is no data supporting this material limitation in the '437 patent, and only two passing references in the patent's specification. EX1001, 5:43-46; 6:53-57; see also Rautio (EX1050), ¶¶63-67; and Meanwell (EX1051), ¶¶100-01. In fact, the '437 patent's provisional application fails to disclose a “half-life  $t_{1/2}$  range of 1-6 minutes,” and at best simply alludes to “fast” permeability and hydrolysis. EX1013, ¶¶00023, 00028; Rautio (EX1050), ¶98. Instead, the '437 patent's later-filed PCT/US2017/060761, filed November 9, 2017, contains the first disclosure of a “half-life  $t_{1/2}$  range from 1-6 minutes.” Rautio (EX1050), ¶¶102-103. Specifically, in paragraphs 00023 and 00028 of later-filed PCT/US2017/060761, the new “half-life of 1-6 minutes” subject matter, absent from the provisional application but now disclosed in the

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<sup>8</sup> WO 2018/08957 (EX1014) is the counterpart to PCT/US2017/060761.

‘437 patent, appears in “**bold**” while the deletions to the corresponding paragraphs of the provisional application are illustrated with “~~strikethroughs~~”:

A pro-drug **is a derivative of epinephrine** selected for fast permeability through sublingual and buccal membranes (*i.e.*, **a compound that dissolves in the oral cavity**) and fast hydrolysis (**half-life  $t_{1/2}$  range from 1-6 minutes**) by plasma enzymes to form epinephrine when delivered. ~~The molecule that shows fast permeability through the sublingual and buccal membrane and fast hydrolysis by the enzyme is a physical property.~~ **These characteristics are physical properties** of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

\*\*\*

~~The molecule that shows~~ **If these molecules show** fast permeability through the sublingual and buccal membranes and fast hydrolysis by the enzyme (**half-life 1-6 minutes**) ~~is~~ a physical property of a compound that is useful to be formulated in a unit dosage form as a rapidly dissolving film.

*Compare* EX1013, ¶¶00023, 00028 *with* EX1014, ¶¶00023, 00028 *and* EX1001, 6:52-57; Rautio (EX1050), ¶¶63-65. Thus, the challenged claims are entitled to an effective filing date of no earlier than November 9, 2017.

## VI. LEVEL OF ORDINARY SKILL IN THE ART

As of the earliest priority date, a POSA would have possessed an advanced degree (*i.e.*, a Ph.D. or equivalent) in fields relevant to drug formulation, and design (*i.e.*, pharmaceutical, medicinal, organic chemistry, or the equivalent), and at least 2-3 years of practical experience in the development, design, and/or synthesis of prodrugs. Alternatively, a POSA could have a lesser educational degree combined with additional practical experience (*i.e.*, 5-6 years) involving research and development related to pharmaceutical compounds, including prodrug formulations. A POSA would have understood the teachings and disclosures of the references identified on Petitioner's Exhibit List and would have been capable of drawing reasonable inferences and conclusions from that prior art. Additionally, a POSA would have understood that activities relating to, *inter alia*, the development, design, synthesis and testing of prodrug formulations often require a multidisciplinary approach. Moreover, a POSA would have been able to draw on, not only his or her own expertise, but also could have also taken advantage of specialized skills of others, through consultation and collaboration, to solve any issues that arise in connection with the development, design, synthesis and/or testing of prodrug formulations. Rautio (EX1050), ¶¶22-25; Meanwell (EX1051), ¶¶39-42.

## VII. CLAIM CONSTRUCTION

With the exception of the term discussed below, all other terms recited in challenged claims 1-3, including the skeletal structure depicted in challenged claims 1-2, should be given their plain and ordinary meanings.

### A. “half-life $t_{1/2}$ ” Claim Construction and Summary Chart

The ‘437 patent does not define “half-life  $t_{1/2}$ ,” and its only references to the quantification of “half-life” is in connection with the 1,800 second half-life in *in vitro* human plasma reported in Table 3 of Truelove 1 for the diester epinephrine prodrug identified as “L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate,” and Truelove 4’s disclosure regarding the *in vitro* hydrolysis of that same epinephrine compound. Truelove 1 (EX1002), 9:15-38; Truelove 4 (EX1007), p.1511; *see* Meanwell (EX1051), ¶¶100-101; Rautio (EX1050), ¶¶106-114 . Specifically, Truelove 1 measured the enzymatic rate of hydrolysis in various media at 37°C to obtain the “ $t_{1/2}$  life,” and reported those results in Table 3. EX1002, 9:15-38; Meanwell (EX1051), ¶103; Rautio (EX1050), ¶109. Additionally, Table 1 of Truelove 4, reports that after 28 minutes (1,680 seconds) the “dipivalyl” compound identified in Table 3 of Truelove 1 had hydrolyzed, and 47.5% epinephrine was released into the plasma. EX1007, p.1511; Meanwell (EX1051), ¶¶104-07; Rautio (EX1050), ¶¶111, 218-222. Thus, Truelove 4

confirms the half-life  $t_{1/2}$  value reported in Table 3 of Truelove 1. Rautio (EX1050), ¶¶111, 221; Meanwell (EX1051), ¶¶96-97, 105. At bottom, the half-life  $t_{1/2}$  values reported in Truelove 1 and Truelove 4 are the same values recited in the challenged claims of the ‘437 patent. Meanwell (EX1051), ¶¶97, 105; *see* Rautio (EX1050), ¶¶114, 221-222.

“Half-life  $t_{1/2}$ ” as recited in the challenged claims should be construed as “the time for one-half of the epinephrine to be formed from its prodrug in human plasma.”<sup>9</sup> *Id.*, ¶114; Meanwell (EX1051), ¶¶108.

| TERM                                | CONSTRUCTION                                                                            |
|-------------------------------------|-----------------------------------------------------------------------------------------|
| Half-life $t_{1/2}$<br>(Claims 1-2) | The time for one-half of the epinephrine to be formed from its prodrug in human plasma. |

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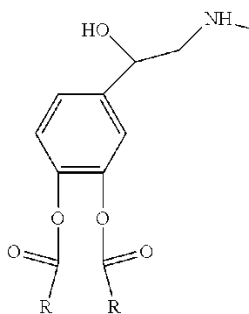
<sup>9</sup> A POSA would have expected the half-life  $t_{1/2}$  values of the salt and non-salt (*i.e.*, free-base) forms of the diester epinephrine compounds disclosed in Truelove 1 and recited in the challenged claims would be the same. Rautio (EX1050), ¶¶114, 135-137, 296-300; Meanwell (EX1051), ¶¶77-79, 108, 111; *infra* pp.39-41.

## VIII. THE CHALLENGED CLAIMS OF THE '437 PATENT

Only claims 1-3 of the '437 patent are subject to this Petition:

### A. Claim 1

A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration of a Formula:



wherein R is selected from the group consisting of:

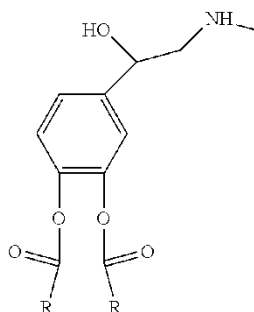
... -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,<sup>[10]</sup> ... or a pharmaceutically acceptable salt thereof, wherein said compound has a Log P value in the range of about 0.5-6.0 and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life  $t_{1/2}$  range from 1-6 minutes.

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<sup>10</sup> This compound corresponds to the structure depicted in Figure 5G” of the ‘437 patent. Rautio (EX1050), ¶¶69, 175, 178-179, 319-320, 324-325; Meanwell (EX1051), ¶38, n.9; *infra* p.38.

**B. Claim 2**

A compound of a Formula



wherein R is selected from the group consisting of: **CH<sub>3</sub>**, **CH<sub>2</sub>CH<sub>3</sub>** and **CH(CH<sub>3</sub>)<sub>2</sub>**<sup>[11]</sup> wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and has a half-life  $t_{1/2}$  range from 1-6 minutes.

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<sup>11</sup> The highlighted compounds correspond to structures depicted in Figures 7A, 7C, and 7B where the R substituents of the ester promoieties are CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and CH(CH<sub>3</sub>)<sub>2</sub>, respectively. Rautio (EX1050), ¶¶69, 143, 149, 156, 178-179, 331-341; Meanwell (EX1051), ¶38, n.10; *infra* p.35-39.

**C. Claim 3**

The compound of claim 2, wherein the compound is selected from the group consisting of: **4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene diacetate**; **4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate)**; **4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene dipropionate**<sup>[12]</sup>; and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.

**IX. THE ‘437 PATENT’S PROSECUTION HISTORY**

The Examiner issued a Non-Final rejection rejecting claims 1, 3, and 19-21 under 35 U.S.C. § 103 as being unpatentable over Rawas-Qalaji (EX1017) in view of Bodor (EX1016). Almoazen File History (EX1005), pdf pp.87-95. Importantly, the Examiner observed that the Log P value of the pending claims was an inherent property of the claimed compounds. EX1005, pdf p.91; Rautio (EX1050), ¶74.

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<sup>12</sup> The highlighted names correspond to the structure depicted in claim 2 where the R substituents of the ester promoieties are CH<sub>3</sub>, CH(CH<sub>3</sub>)<sub>2</sub>, and CH<sub>2</sub>CH<sub>3</sub>, respectively. Rautio (EX1050), ¶¶69, 142, 149, 156, 178-179; Meanwell (EX1051), ¶38, n.11-13; *infra* pp.35-39.

The Examiner also found that Rawas-Qalaji taught injectable epinephrine also delivered in other suitable forms, including buccal and sublingual films. EX1005, pdf p.91; Rautio (EX1050), ¶75.

In its response, Applicant did not contest that the Log P values were an inherent property of the claimed compounds. EX1050, ¶77. Additionally, relying on a 2-page, 5-paragraph Declaration, Applicant contended there was long-felt need for an alternative to injectable epinephrine. EX1050, ¶78; EX1005, pdf pp.75-76. The Examiner, however, rejected Applicant's arguments, determined that Applicant failed to provide any objective evidence of long-felt need, and issued a Final Rejection. EX1005, pdf pp.59-68; EX1050, ¶78.

Responding to the Examiner's Final Rejection, Applicant amended pending claims 1 and 19 (ultimately issued as claims 1 and 2) by adding the limitation: "wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and **has a half-life  $t_{1/2}$  range from 1-6 minutes.**" EX1005, pdf pp.39-51; Rautio (EX1050), ¶79. Applicant argued ¶00023 of the pending application provided support for this amendment. EX1005, pdf 30, p.5; Rautio (EX1050), ¶80. However as detailed previously, ¶00023 of the '437 patent's provisional application (EX1013, p.20) did not disclose a "half-life  $t_{1/2}$  range from 1-6

minutes.” *Supra* pp.14-15. Applicant also attempted to refute the obviousness rejection by *sua sponte* directing the Examiner to the Truelove references cited in the “Description of Related Art Including Information” section of the ‘437 patent (*see* EX1001, 2:5-39) and Truelove 1’s 30 minute half-life  $t_{1/2}$  disclosure (*see* EX1002, 9:28-37). EX1005, pdf pp.47-48. However, by only singling out this 30 minute half-life  $t_{1/2}$ , while turning a blind-eye to the diester epinephrine compounds disclosed in Truelove 1 with half-life  $t_{1/2}$  values of 1-6 minutes, Applicant disingenuously argued that the pending claims were patentable and mislead the Examiner. Rautio (EX1050), ¶81.

Importantly, the Examiner never cited or addressed Truelove 1 (Exhibit 1002), or for that matter any of the other Truelove references mentioned in the ‘437 Patent (Exhibits 1002, 1006 and 1007). Additionally, the Examiner never challenged or even referred to Almoazen’s characterizations of Truelove 1. Instead, the Examiner simply accepted and relied on Almoazen’s misleading arguments regarding Truelove 1 as the basis for withdrawing the rejections. *Id.*, ¶¶8-89.

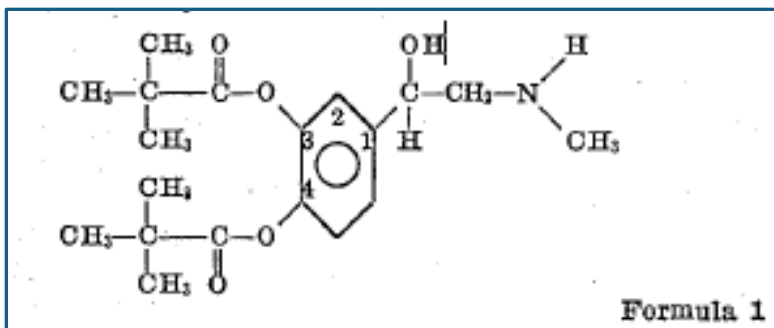
Moreover, the Examiner in allowing the claims to issue also relied on her erroneous interpretation of Figure 9 to the effect that it showed that Almoazen’s

prodrug compound had a half-life falling within the claimed 1-6 minutes. Contrary to the Examiner's understanding, EX1001, Figure 9 does not disclose an epinephrine prodrug, but merely discloses how fast epinephrine *per se* is released from an Almoazen film which contains only epinephrine (not an epinephrine prodrug) in simulated saliva, not human plasma. *Id.*, ¶90. See Statement of Allowance, Exhibit 1005, pdf. p. 14.

## **X. PRIOR ART**

### **A. Truelove 1 (EX1002)**

U.S. Patent No. 3,809,714 ("Truelove 1"), entitled "Novel Ester of [(Methylamino)-methyl]benzyl Alcohol," issued on May 7, 1974, describes "a novel and useful therapeutic ester of benzyl alcohol", and discloses comparative diester epinephrine compounds in Table 3. *See e.g.*, Truelove 1 (EX1002), 1:28-30; 9:26-38. Specifically, Truelove 1 provides the new compound's skeletal structure, and states that this diester epinephrine compound has "improved lipid solubility for enhanced resorption when administered. . . ."



EX1002, 1:15-21; 1:33-41; 2:28-39; 2:50-58; 5:69-75; 9:15-25; 10:9-16; *see generally* Rautio (EX1050), ¶¶116-179; Meanwell (EX1051), ¶¶44-91. Truelove 1 also teaches that this diester epinephrine compound could be administered using “buccal patches,” and discloses the inclusion of various “pharmaceutically acceptable carriers.” EX1002, 1:45-48; 6:29-45; 6:59-64.

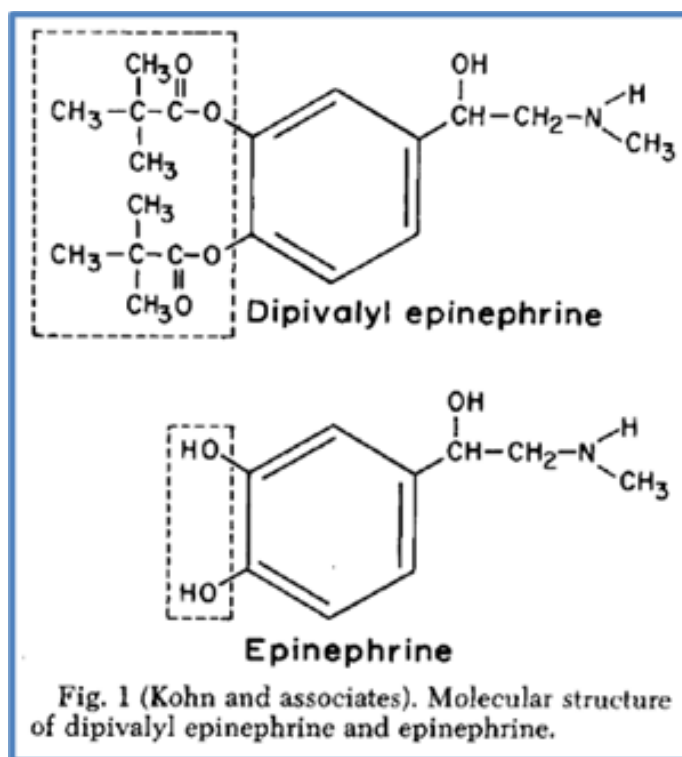
Table 3 discloses four diester epinephrine compounds with different promoieties, including the “dipivalyl” compound identified as the “novel ester compound”, and reports the rate of enzymatic hydrolysis (*e.g.*, “the  $t_{1/2}$  life”) in human plasma for each compound. Importantly, Table 3 reports that three diester epinephrine compounds have a half-life range from 1-6 minutes as recited in the challenged claims.

| TABLE 3                                                                                      |                                                 |        |       |
|----------------------------------------------------------------------------------------------|-------------------------------------------------|--------|-------|
| Compound                                                                                     | Rate of hydrolysis in<br>$t\frac{1}{2}$ seconds |        |       |
|                                                                                              | Horse                                           | Rabbit | Human |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperechlorate.....    | 20                                              | 45     | 180   |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperechlorate..... | 50                                              | 90     | 240   |
| L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperechlorate.....   | 100                                             | 160    | 360   |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl]<br>benzyl alcohol hydroperechlorate.....   | 600                                             | 720    | 1,800 |

EX1002, 9:26-38; *see* Rautio (EX1050), ¶127; Meanwell (EX1051), ¶63.

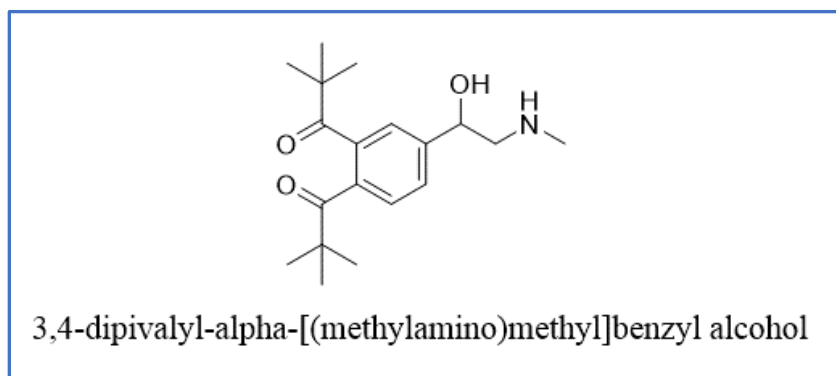
### 1. The Compounds Identified in Truelove 1 are Incorrectly Named

The correct name of the Formula 1 skeletal structure of the diester epinephrine compound identified as “the present invention” is “3,4-**dipivaloxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol.” Rautio (EX1050), ¶¶120-122; Meanwell (EX1051), ¶¶51, n.14, 64-69. However, Truelove 1 incorrectly uses “**dipivalyl**” instead of “**dipivaloxy**,” to identify this diester epinephrine compound. *See, e.g.*, EX1002, 9:36-37; 10:18-21. Nevertheless, detailing the synthesis of the inventive compound, Truelove 1 correctly identifies this compound, depicted by Formula 1, by an alternative name: “l-dipivalylepinephrine.” EX1002, 5:15-21. Notably, EX1044 confirms the structure of “dipivalyl epinephrine” (*i.e.*, “dipivalylepinephrine”) is identical to the structure of Truelove 1’s Formulas 1 and 8.



Meanwell (EX1051), ¶53-54, 71-72; Rautio (EX1050), ¶¶120-121.

A POSA would have also known the name Truelove 1 attributes to the Formula 1 structure (*i.e.*, 3,4-**dipivalyl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol) is wrong and corresponds to a ketone derivative having the following structure:



Rautio (EX1050), ¶¶121-122, 163-165; Meanwell (EX1051), ¶¶55-56, 73, 88-89.

Importantly, a POSA would have understood that ketone derivatives of epinephrine cannot function as a prodrug because of their inability to metabolize in human plasma and therefore are incapable of having a half-life  $t_{1/2}$  that results in the formation of epinephrine. *See, e.g.*, Rautio (EX1050), ¶¶141, 148, 163, 173; *see* Meanwell (EX1051), ¶75. Truelove 1's nomenclature errors would have also been obvious to a POSA because Truelove 1:

- is entitled “**Novel Ester** of [(methylamino)-methyl]benzyl alcohol . . . .” EX1002, 1:2-3;
- recites “[a] **novel ester** of [Formula 1]” *Id.*, 1:12-21;
- declares “[t]he present invention relates to both **a novel and useful therapeutic ester** of benzyl alcohol . . . and pertains to a new compound **represented by Formula 1.**” *Id.*, 1:28-42;
- states “another object of the invention is to provide **a novel and useful physicochemical ester** of . . . and its acceptable salts.” *Id.*, 2:18-20; and
- discloses the synthesis of the recited compounds is predicated on esterification. *Id.*, 3:16-21 (“the hydroxyl groups

. . . are **esterified**. . . . Examples of acylating agents suitable for **esterifying** the hydroxyl groups. . . .”).

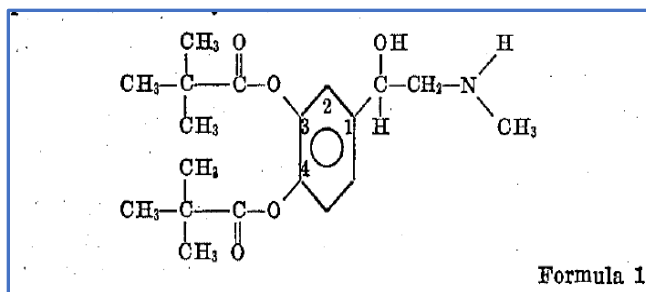
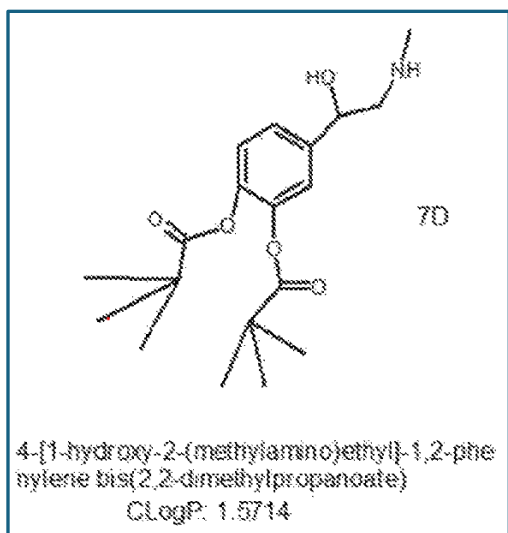
See Meanwell (EX1051), ¶¶45-58, 64-76; Rautio (EX1050), ¶¶117-119, 123-124, 128, 131.

Instructive is *Forest Labs, Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1271 (Fed. Cir. 2007) where the Federal Circuit noted a POSA would correct an “immediately apparent” error “to be consistent with the disclosure of the specification.” See *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011) (POSA interprets prior art references “using common sense and appropriate perspective”). Accordingly, a POSA would have recognized Truelove 1’s nomenclature mistakes and understood that Table 3 actually discloses diester epinephrine compounds. See, e.g., Rautio (EX1050), ¶¶128, 130-131, 138, 140-153, 155-161, 163-167, 170-179; Meanwell (EX1051), ¶¶64-76, 80-82, 84, 86, 88, 90.

Additionally, Truelove 4, an article authored by Truelove 1’s named inventors, correctly identifies the inventive diester of Truelove 1 as “3,4-dipivaloxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol” EX1007, p.1510 & n.1; see Rautio (EX1050), ¶¶111, 129, 218-219; Meanwell (EX1051), ¶¶92-94.

Perhaps most telling, the ‘437 patent recognizes Truelove 1 discloses a number of diester epinephrine compounds. For example, the structures depicted in Figures 7A-7D of the ‘437 patent correspond to diester epinephrine compounds disclosed in Truelove 1. *See, e.g.*, EX1001, 2:11-12 (Truelove 1 “synthesized four different prodrugs . . . (see structures 7A, 7B, 7C, 7D)”; 4:9-10 (“FIG. 7 shows [Truelove 1’s] compounds.”); *supra* pp.8-13.

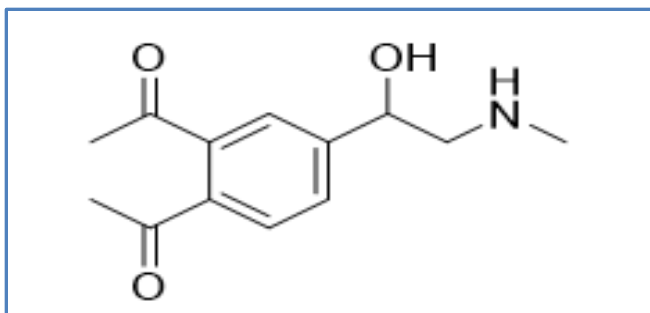
In fact, the ‘437 patent correctly identifies Truelove 1’s compounds as diester epinephrine compounds, not ketone derivatives, and provides the corresponding diester structures. *See* Meanwell (EX1051), ¶¶34-37, 80-81; Rautio (EX1050), ¶¶54-60, 133-134, 178-179. For example, after referring to Truelove 1’s “3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydrochloride,” Figure 7D of the ‘437 patent, reproduced in the box on the left, provides that compound’s skeletal structure which is the same structure depicted by Formula 1 of Truelove 1, reproduced in the box on the right.



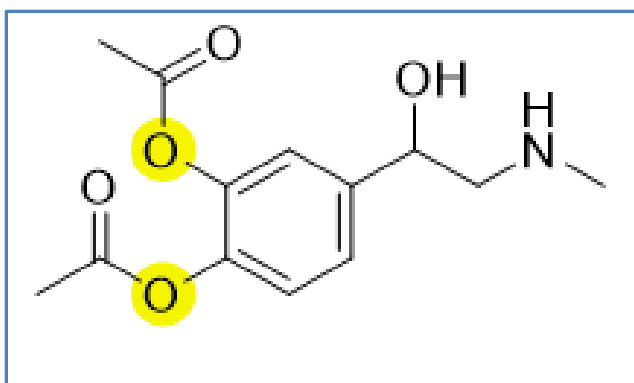
Compare EX1001, Figure 7D with EX1002, Formula 1, 2:50-58.

A POSA would have also known that the names of the other “ $\alpha$ -[(methylamino)-methyl]benzyl alcohol” derivatives identified in Table 3 (3,4-diacetyl; 3,4-dipropionyl; 3,4-dibutyryl) mistakenly correspond to ketone derivatives. Nevertheless, a POSA would have understood that Table 3 actually discloses diester epinephrine compounds (3,4-diacetoxy; 3,4-dipropionyloxy; 3,4-dibutyroxy). Rautio (EX1050), ¶¶130, 138-151, 171-179; Meanwell (EX1051), ¶¶59-61, 64-76, 80-82, 84, 90.

For example, Table 3’s “L-3,4-**diacetyl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate” is erroneously identified as a ketone derivative having the following non-salt (*i.e.*, free-base) structure:



A POSA, however, would have known this ketone derivative could not function as an epinephrine prodrug because it is missing two (2) oxygen molecules highlighted below, and therefore would be incapable of having a half-life  $t_{1/2}$  because it was unable to rapidly metabolize in human plasma into the epinephrine:



Rautio (EX1050), ¶¶141-142; Meanwell (EX1051), ¶75.

After only a cursory review of Truelove 1, a POSA would have:

- known the compound identified as “L-3,4-**diacetyl**-α-[(methylamino)-methyl]benzyl alcohol hydroperchlorate” in Table 3 was misnamed;
- ignored Truelove1’s obvious nomenclature error; and

- substituted the proper diester name in its place: “L-3,4-**diacetoxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate.”

Rautio (EX1050), ¶¶138-145; Meanwell (EX1051), ¶¶59-60, 76, 80-82; *see Forest Labs*, 501 F.3d at 1271 (POSA would correct an “immediately apparent” error).

For the same reasons, a POSA would have understood that Table 3 also incorrectly identifies “L-3,4-**dipropionyl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate” and “L-3,4-**dibutyryl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate” as ketone derivatives, but that Truelove 1 actually teaches “L-3,4-**dipropionoxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate” and “L-3,4-**dibutyroxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate.” Rautio (EX1050), ¶¶146-151, 170-178; Meanwell (EX1051), ¶¶59-60, 76, 80-81, 84, 90.

Further confirming a POSA’s recognition of Truelove 1’s nomenclature mistakes, the ‘437 patent depicts the structures of the compounds disclosed in Truelove 1’s Table 3 as diester epinephrine compounds. *See* EX1001, Figures 5G”, 7A-7D. The ‘437 patent also provides the alternative names for those correctly identified diester compounds. EX1001, Figures 5G”, 7A-7D; 6:42-52; 6:58-68; *see supra* p.12-13; *infra* pp.26-41.

Based on the totality of Truelove 1's disclosure, Truelove 4's correction of Truelove 1's naming error, and the '437 patent's recognition of Truelove 1's obvious nomenclature mistakes, a POSA would have recognized Truelove 1's errors, ignored those mistakes, and substituted in their place the correct names of the disclosed diester epinephrine compounds. *See, e.g.*, Rautio (EX1050), ¶¶128-134, 138-179; Meanwell (EX1051), ¶¶51, n.14, 64-76, 80-82, 84, 86, 88, 90.

Instructive is *In re Yale*, 434 F.2d 666, 668 (C.C.P.A. 1970), where the Court found the identification of "CF<sub>3</sub>CF<sub>2</sub>CHClBr" was an error and concluded that this error "would be apparent" to a POSA who would have "mentally substituted" the correct formula "in its place." Similarly, in *LG Elecs. Inc. v. Immervision, Inc.*, 39 F.4th 1364, 1373 (Fed. Cir. 2022), the Federal Circuit, relying on *In re Yale*, agreed with the PTAB that the prior art contained "an obvious error . . . that would have been apparent to one of ordinary skill in the art, who would have substituted it with the correct information. . . ."

## **2. Chart 2 - Summary of Truelove 1's Disclosure of Diester Epinephrine Compounds**

Chart 2 summarizes Truelove 1's disclosure of the diester epinephrine compounds recited in challenged claims 1-3.<sup>13</sup>

The first column details:

- a POSA's understanding of the diester epinephrine compounds disclosed in Truelove 1;
- ChemDraw<sup>®</sup>'s structural representation of those compounds;<sup>14</sup>
- the R substituents of the compounds' ester promoieties; and
- the compounds' half-life  $t_{1/2}$  values in seconds.

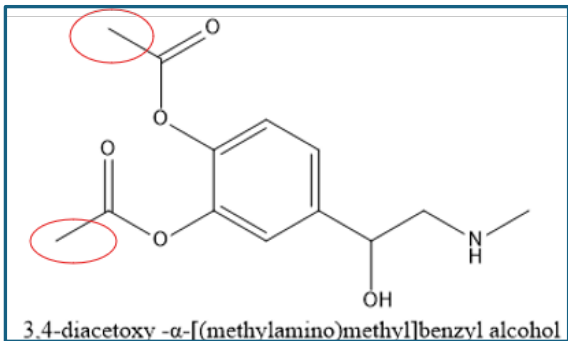
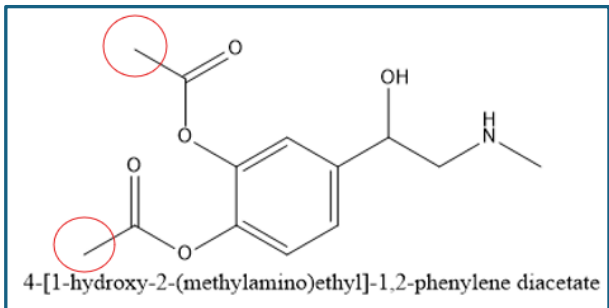
The second column provides:

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<sup>13</sup> For more detailed Truelove 1 disclosure charts, see Rautio (EX1050), ¶178; and Meanwell (EX1051), ¶80.

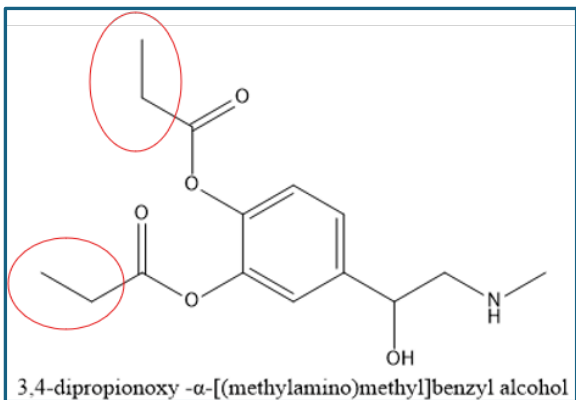
<sup>14</sup> Any orientational differences in respective structures result from ChemDraw<sup>®</sup>'s naming algorithms, and the structures in individual rows correspond to the same diester epinephrine compound. *See* Meanwell (EX1051), ¶¶70, 80-81; Rautio (EX1050), ¶¶29, 179.

- the '437 patent's equivalent names for the diester epinephrine compounds disclosed in Truelove 1;
- ChemDraw<sup>®</sup>'s structural representation of those compounds;
- the Figures of the '437 patent depicting those Truelove 1 compounds; and
- the claims of the '437 patent that recite those compounds.

| CHART 2                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>3,4-di<del>acetyl</del>acetoxy-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p>  <p>3,4-diacetoxy -<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p> <p>R = CH<sub>3</sub><br/>t<sub>1/2</sub> = 180 seconds</p> | <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate</p>  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate</p> <p>Figure 7A<br/>Claims 2-3</p> |

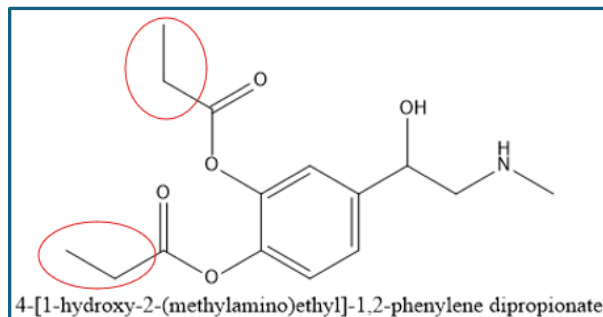
## CHART 2

3,4-di~~propionyl~~propiony- $\alpha$ -  
[(methylamino)methyl]benzyl alcohol



$R = CH_2CH_3$   
 $t_{1/2} = 240$  seconds

4-[1-hydroxy-2-(methylamino)ethyl]-  
1,2-phenylene dipropionate



## ALTERNATIVELY

4-[1-hydroxy-2-(methylamino)ethyl]-  
1,2-phenylene dipropionate

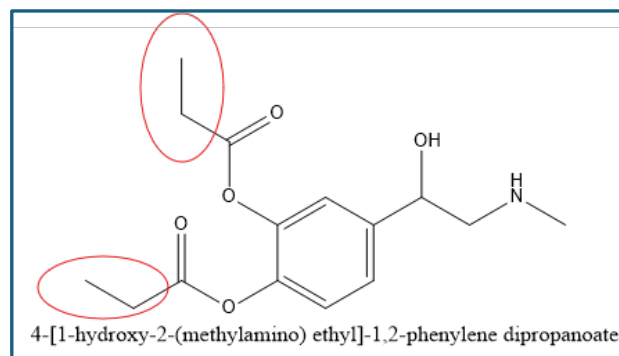
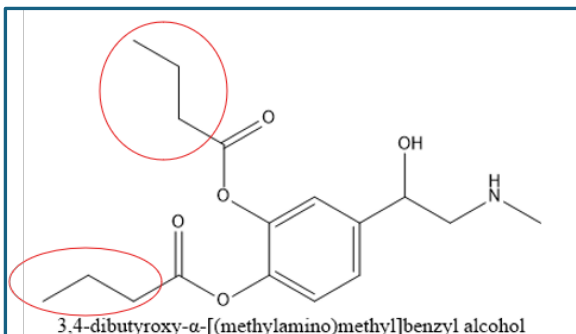


Figure 7C  
Claims 2-3

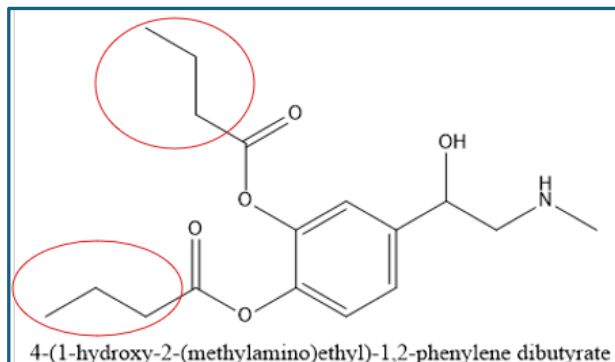
## CHART 2

3,4-~~di~~**butyryl**butyroxy- $\alpha$ -  
[(methylamino)methyl]benzyl alcohol



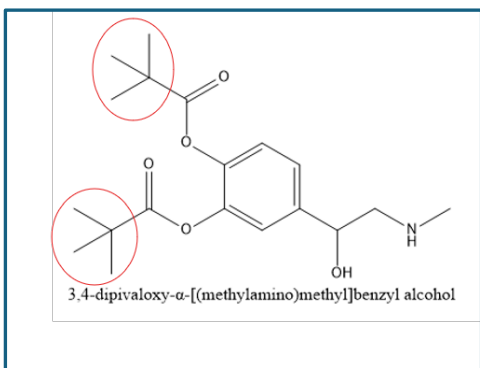
R = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>  
t<sub>1/2</sub> = 360 seconds

4-(1-hydroxy-2-(methylamino)ethyl)-  
1,2-phenylene dibutyrate



Claim 1  
Figure 5G''

3,4-~~di~~**pivalyl**pivaloxy- $\alpha$ -  
[(methylamino)methyl]benzyl alcohol



R = C(CH<sub>3</sub>)<sub>3</sub>  
t<sub>1/2</sub> = 1800 seconds

4-(1-hydroxy-2-(methylamino)ethyl)-  
1,2-phenylene bis(2,2-  
dimethylpropanoate)

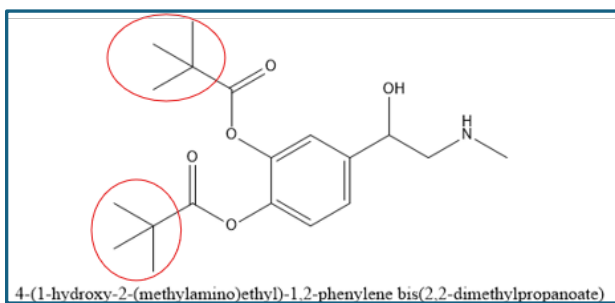
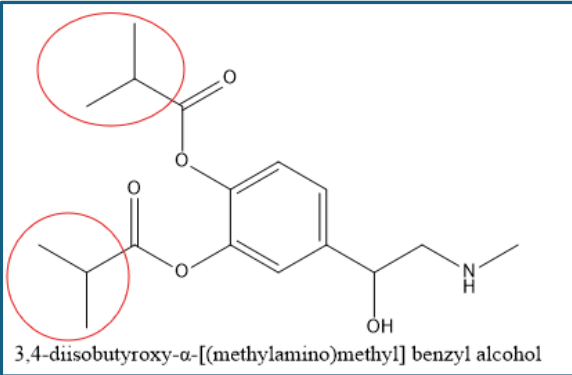
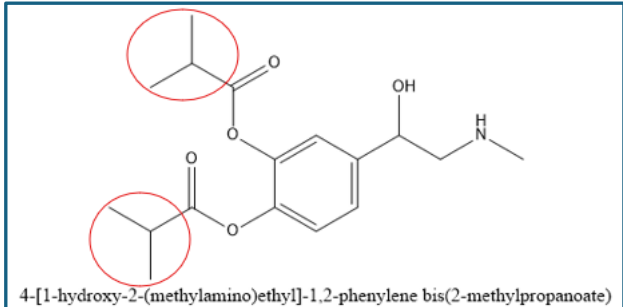


Figure 7D  
Not claimed

| CHART 2                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>3,4-diisobutyrylisobutyroxy<br/>-<math>\alpha</math>-[(methylamino)methyl] benzyl<br/>alcohol</p>  <p>3,4-diisobutyroxy-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol</p> <p><math>R = \text{CH}(\text{CH}_3)_2</math></p> | <p>4-[1-hydroxy-2-(methylamino)ethyl]-<br/>1,2-phenylene bis(2-methylpropanoate)</p>  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene bis(2-methylpropanoate)</p> <p>Fig. 7B</p> |

See Meanwell (EX1051), ¶¶80-91; Rautio (EX1050), ¶¶178-179.

### 3. The Half-Life $t_{1/2}$ of Salt and Non-Salt Forms of the Diester Epinephrine Compounds Would Be The Same

The inclusion of the term “hydroperchlorate” indicates that the compounds of Table 3 of Truelove 1 are the corresponding salt forms of the disclosed diester epinephrine compounds. Rautio (EX1050), ¶135; Meanwell (EX1051), ¶¶77-79. A POSA would have expected that, upon dissolution of the salt and non-salt (*i.e.*, free-base) forms of these compounds in human plasma, the compound’s respective enzyme-mediated cleavage rates, and the formation of the parent epinephrine

compound, would not be affected. That is, the half-life  $t_{1/2}$  of both the salt and free-base forms would have been expected to be essentially the same. Rautio (EX1050), ¶¶135-137, 139-141, 146-148, 161-163, 171-173, 288, 296-297; Meanwell (EX1051), ¶¶77-79, 82-85, 90-91, 108, 111; *see Forest Labs, LLC v. Sigma Pharm Labs.*, 257 F. Supp. 3d 664, 692 (D. Del. 2017) (POSAs “familiar with sublingual and buccal compositions know that . . . asenapine maleate will disassociate from its salt leaving asenapine free-base, which will cross the oral mucosa [and] enter the blood stream”, and “would understand that the inventors actually invented the subject matter recited . . . including the free base form . . . because it is this form that provides the therapeutic affect”); *Eli Lilly & Co. v. Zenith Goldline Pharms, Inc.*, 364 F. Supp. 2d 820, 848 (S.D. Ind. 2005), *aff’d*, 471 F3d 1369 (Fed. Cir. 2006) (“The difference between a . . . salt and a free base is just their physical forms. . . . It is the same molecule in both forms”, and “the form (salt or free base) does not fundamentally change the pharmacological action”).

In sum, a POSA would have expected that the half-life values for the “hydroperchlorate” compounds reported in Table 3 to be for all practical purposes the same as the corresponding non-salt compounds. Rautio (EX1050), ¶¶135-137, 139-141, 146-148, 161-163, 171-173; Meanwell (EX1051), ¶¶77-79, 108, 111.

Truelove 1 was not discussed or applied by the Examiner during the prosecution of the '437 patent.

**B. The Almoazen Paper (EX1022)**

The Almoazen Paper was authored by the named inventor of the '437 patent, Hassan Almoazen, and five other co-authors. EX1022. The Almoazen Paper (EX1022) was published on January 6, 2016, more than a year before '437 Patent's earliest effective filing date of November 9, 2017. The Almoazen Paper states that the “study presents potential proof for using FDFs [fast dissolving films] as a replacement therapy of epinephrine injections,” and teaches epinephrine compounds formulated in a fast dissolving film in a unit dosage form (*i.e.*, a dose range of 5mg-30mg of epinephrine) for buccal administration. EX1022, pp.1012-13 (“Volunteers were asked to place the film on the interior surface of their buccal cavity.”). The Almoazen Paper also notes “excipients” could be added to epinephrine prior to forming the FDFs. EX1022, p.1013 (“Other excipients and epinephrine HCl were added to the solutions. . . .”). See generally, Rautio (1050), ¶¶180-192.

The '437 patent and the Almoazen Paper disclose identical information regarding unit dosage forms of epinephrine configured for sublingual or buccal

administration in rapidly or fast dissolving films. Rautio (EX1050), ¶182. For example, at least the following portions of the ‘437 patent appear to have been copied almost verbatim from the Almoazen Paper. EX1001, Figures 8-9; 1:40-44; 4:11-15; 7:41-8:4; 8:8-33; 8:43-11:55; *see* Rautio (EX1050), ¶¶183-186. Additionally, Tables 3-5 and Figures 8-9 of the ‘437 patent are copies of Tables 1-3 and Figures 1-2 of the Almoazen Paper. EX1002, ¶¶185-186.<sup>15</sup>

Applicant never disclosed the Almoazen Paper to the Patent Office. EX1002, ¶¶180, 192.

**C. Ashraf (EX1003)**

Ashraf, entitled “Considerations in Developing Sublingual Tablets - An Overview,” discusses the physicochemical properties of drugs. EX1003. Specifically, Ashraf teaches that “[s]atisfactory oral [mucosal] absorption of drugs has been observed over a wide range of log P (octanol/water partition coefficient) values of 1 to 5.” EX1003, p.35; *see* Rautio (EX1050), ¶¶193-196. Notably, the ‘437 patent acknowledges that Log P values of 0.5-6.0 are disclosed in Ashraf and

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<sup>15</sup> Prepared by Dr. Rautio, EX1033 highlights portions of the ‘437 patent copied from the Almoazen Paper. EX1002, ¶184. EX1035 does the reverse. *Id.*

concedes that the Log P value of a diester epinephrine compound where the R substituents of the ester promoieties are  $\text{CH}_2\text{CH}_2\text{CH}_3$  is 0.8. EX1001, 5:7-30; 7:11-18. See generally, Rautio (1050), ¶¶193-196.

Ashraf was not discussed or applied by the Examiner.

**D. Fuchs (EX1004)**

U.S. Patent No. 4,136,145 (“Fuchs”) is entitled “Medicament Carriers in the Form of Film Having Active Substance Incorporated Therein.” EX1004. The ‘437 patent concedes that Fuchs discloses “[f]ilms that incorporate a pharmaceutically active ingredient” and describes administration of those films to “mucosal membrane areas of the body, including the mouth. . . .” EX1001, 2:39-47. Fuchs also teaches compositions and methods for making the unit dosage films. EX1004, 2:65-5:6. Further, Fuchs discloses that “a pharmaceutically active medicament compound” can be “dissolved or uniformly dispersed in a flexible, water-soluble film carrier” and “drawn into a film, which can be cut to desired unit dosage content.” EX1004, Abstract; 1:10-14; *see* Rautio (EX1050), ¶¶197-200.

Fuchs was not discussed or applied by the Examiner.

**E. Truelove 3 (EX1008)**

U.S. Patent No. 3,868,461 (“Truelove 3”), entitled “Ester of 3,4-Dihydroxy-Alpha (Isopropylamino) Methyl Benzyl Alcohol, Composition and Anti-Asthma Use Thereof”, discloses diesters of 3,4-dihydroxy- $\alpha$ -(isopropylamino) methyl]benzyl alcohol, commonly known as “isoproterenol.” *See, e.g.*, EX1008, 1:7-30. *See generally*, Rautio (1050), ¶¶201-216.

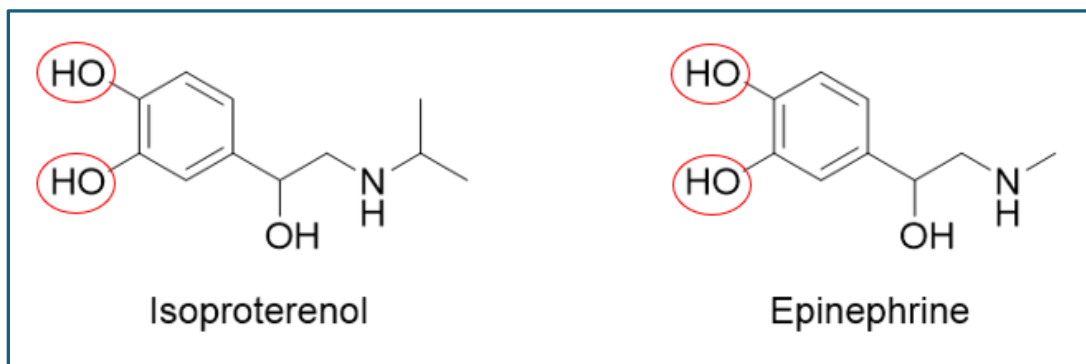
Truelove 3 teaches administration by “buccal patches” and describes the use of various “pharmaceutically acceptable carriers.” EX1008, 7:32-50.

Additionally, Truelove 3 uses the same methodology as Truelove 1 to determine half-life  $t_{1/2}$  (*compare id.*, 10: 50-57 with EX1002, 9:18-24), and reports the half-life values of several diester isoproterenol compounds:

| TABLE 3                                                                            |                                            |        |       |
|------------------------------------------------------------------------------------|--------------------------------------------|--------|-------|
| Compound                                                                           | Rate of Hydrolysis<br>in $t_{1/2}$ Seconds |        |       |
|                                                                                    | Horse                                      | Rabbit | Human |
| 3,4-diacetoxy- $\alpha$ [(isopropylamino)-methyl]benzyl alcohol hydrochloride      | 20                                         | 45     | 180   |
| 3,4-dipropionyloxy- $\alpha$ [(isopropylamino)-methyl]benzyl alcohol hydrochloride | 50                                         | 90     | 240   |
| 3,4-dibutyroxy- $\alpha$ [(isopropylamino)-methyl]benzyl alcohol hydrochloride     | 100                                        | 160    | 360   |
| 3,4-dipivaloxy- $\alpha$ [(isopropylamino)-methyl]benzyl alcohol hydrochloride     | 600                                        | 720    | 1800  |

EX1008, 10:59-70; *see* Rautio (EX1050), ¶¶202-205.

Not only are isoproterenol and epinephrine structurally similar, but the same hydroxyl groups of each compound are often modified by attaching the same ester promoieties.



Rautio (EX1050), ¶¶203, 206, 211.

For example, the diester isoproterenol compounds disclosed in Table 3 of Truelove 3 have the same ester promoieties as the diester epinephrine compounds disclosed in Table 3 of Truelove 1. Rautio (EX1050), ¶¶205-206, 208-209, 211.

Given this close structural similarity, a POSA would have expected that isoproterenol and epinephrine compounds with the same ester promoieties would have the same half-life  $t_{1/2}$  values. Rautio (EX1050), ¶¶211-214. In fact, a comparison of the compounds and half-life values reported in Truelove 1 and Truelove 3 confirms that isoproterenol and epinephrine compounds with the same ester promoieties have the same half-life  $t_{1/2}$  values. *Compare* EX1002, 9:27-37

with EX1008, 10:58-70; Rautio (EX1050), ¶¶208-209, 211-216; *see Valeant Pharms. Int'l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 32 (Fed. Cir. 2020) (“[o]ur case law reflects an understanding that skilled artisans can expect structurally similar compounds to have similar properties”); *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384-85 (Fed. Cir. 2018) (“similarity in properties can be inferred from structural similarity”).

Truelove 3 was not discussed or applied by the Examiner.

**F. Florence (EX1015)**

Florence, entitled “Physicochemical Principles of Pharmacy,” provides guidance on optimal log P values for various absorbing membranes. EX1015. Table 9.1 of Florence indicates that the ideal log P (*i.e.*, optimum log P) values for buccal absorption typically range from 3.52 to 5.52. *Id.*, p.350. A POSA would have understood Log P values outside of this “ideal” range could still effectively permeate across the mucosal membrane. *See* Rautio (EX1050), ¶¶223-226.

**G. Schobel (EX1021)**

U.S. Patent No. 11,191,737 B2 (“Schobel”), entitled “Enhanced Delivery Epinephrine Compositions”, claims the benefit of a provisional application 62/331,996 filed on May 5, 2016 and qualifies as prior art as of that date under 35

U.S.C. § 102(a)(2) and 35 U.S.C. § 100(i)(1)(B). Schobel discloses the “oral mucosa” is “a convenient route for delivery drugs,” and teaches that drug delivery through the buccal mucosa is limited by the barrier nature of the epithelium and that prodrugs may be employed to overcome this barrier. EX1021, 5:8-13; 6:41-43; 7:26-33; Rautio (EX1050), ¶¶233-237. Additionally, Schobel describes ester prodrugs of epinephrine. *See, e.g.*, EX1021, 15:62-65 (“a composition including epinephrine or its salts or esters can have a biodelivery profile similar to that of epinephrine administered by injection”; 45:19-20 (claim 1) (“a pharmaceutically active component including epinephrine, a pharmaceutically acceptable salt or ester thereof”); *see* 46:45-46 (claim 27); 46:58-59 (claim 28); *see* Rautio (EX1050), ¶¶236-239.

**XI. GROUNDS 1-3 PROVIDE MORE THAN A REASONABLE  
LIKELIHOOD THAT EACH CHALLENGED CLAIM IS  
UNPATENTABLE**

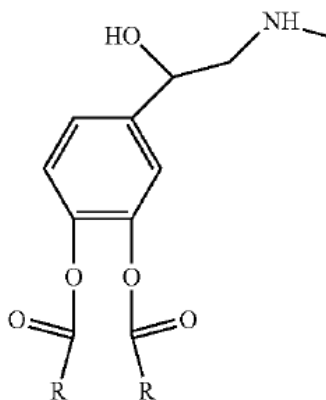
A discussion of Grounds 1-3 for the invalidation of challenged claims 1-3 is detailed below. Petitioner notes that the absence of an entry in the Claim Chart is not an admission that a given reference does not disclose a particular claim element.

**A. Ground 1: Truelove 1, Ashraf, and Almoazen Paper [Claims 1-3]****1. Claim 1**

*[i] “A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration”*

Truelove 1 teaches diester epinephrine compounds that can be administered using “buccal patches.” EX1002, 6:29-32. Additionally, the Almoazen Paper discloses “a dose range of 5mg to 30mg” of epinephrine administered to the “buccal cavity.” EX1022, pp.1012-13 (“Volunteers were asked to place the film on the interior surface of this buccal cavity.”).

*[ii] “of a Formula:*



*wherein R is selected from the group consisting of . . . -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> . . . or a pharmaceutically acceptable salt thereof,”*

Table 3 of Truelove 1 discloses “L-3,4-**dibutyryl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate.” EX1002, 9:26-38. A POSA would have understood the term “dibutyryl” signifies that the R substituents of the ester promoieties of this compound are  $\text{CH}_2\text{CH}_2\text{CH}_3$ . Rautio (EX1050), ¶¶171, 176, 178-179; Meanwell (EX1051), ¶¶38, n.9, 80-81, 90-91, 109. It would have been apparent to a POSA that Truelove 1 misnames this compound a ketone derivative (*i.e.*, “dibutyryl”), not an ester derivative (*i.e.*, “dibutyroxy”). *Supra* pp.12-13, 26-39. Accordingly, a POSA would have:

- recognized this obvious nomenclature error;
- disregarded Truelove 1’s mistake; and
- substituted in its place the correct name of the disclosed diester epinephrine compound: L-3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate.

Rautio (EX1050), ¶¶170, 172-179, 319-324; Meanwell (EX1051), ¶¶80, 90, 109; *see LG Elecs.*, 39 F.4th at 1373 (POSA would have ignored an obvious error and “substituted it with the correct information”); *In re Yale*, 434 F.2d at 668 (error “would be apparent” to a POSA who would have “mentally substituted” the correct formula “in its place”).

In sum, a POSA would have understood that L-3,4-**dibutyryl**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate identified in Table 3 of Truelove 1 was misnamed, but in fact actually discloses L-3,4-**dibutyroxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, which corresponds to the structure recited in claim 1 where both R substituents are **CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>**. Rautio (EX1050), ¶¶170, 172-179, 319-324; Meanwell (EX1051), ¶¶80, 90, 109.

*[iii] “wherein said compound has a log P value in the range of about 0.5 -6.0”*

Ashraf teaches that satisfactory mucosal delivery of drugs occurs when a compound’s log P value is 1-5. EX1003, p.35; EX1050, ¶¶195-196; *supra*, pp.42-43. Additionally, the ‘437 patent acknowledges that the inherent log P of a compound having an ester promoiety where the R substituents are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> is 0.8. EX1001, 5:29; 7:11-18.

*[iv] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

The Almoazen Paper discloses administration of “a dose range of 5mg to 30mg” of epinephrine incorporated into a “fast dissolving film.” EX1022, pp.1012-13, 1015; *supra*, pp.41-42.

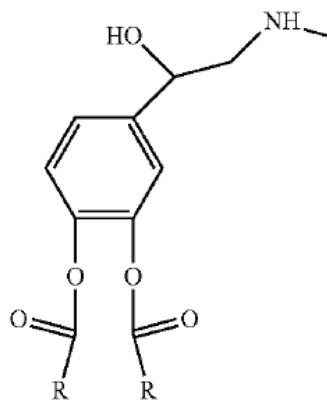
*[v] “and has a half-life range from 1-6 minutes.”*

Table 3 of Truelove 1 reports that the misnamed compound, L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, has a half-life  $t_{1/2}$  of 6 minutes. EX1002, 9:26-38. Nevertheless, a POSA would have known, despite Truelove 1’s nomenclature error, Table 3 discloses the diester epinephrine compound, “L-3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate” which, according to Table 3, has a half-life  $t_{1/2}$  of 6 minutes. Rautio (EX1050), ¶¶170, 172-179; Meanwell (EX1051), ¶¶80-81, 90-91, 109; *supra* pp.33, 38.

The compound recited in claim 1 would have been obvious under 35 U.S.C. § 103 based on the teachings of Truelove 1, Ashraf, and the Almoazen Paper. Rautio (EX1050), ¶¶6(A), 288-298, 308-311, 315-329, 415.

## **2. Claim 2**

*[i] “A compound of a Formula:*



*wherein R is selected from the group consisting of:*

*CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and . . .”*

Table 3 of Truelove 1 discloses L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate and L-3,4-dipropionyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate. EX1002, 9:26-38. A POSA would have understood the terms “diacetyl” and “dipropionyl” signify that the R substituents of the ester promoieties of these compounds are CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub>, respectively. Rautio (EX1050), ¶¶138, 140-144, 146, 148-151, 178-179, 333-335; Meanwell (EX1051), ¶¶36, n.5, 7, 80-83, 84, 109. However, a POSA would have also:

- recognized Truelove 1 misidentifies Table 3’s “diacetyl” and “dipropionyl” compounds as ketone derivatives;
- ignored the incorrectly named compounds (i) L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate and (ii) L-

3,4-dipropionyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol  
hydroperchlorate; and

- substituted in their place the correct names: (i) L-3,4-**diacetoxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, and (ii) L-3,4-**dipropionoxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate.

Rautio (EX1050), ¶¶138, 140-144, 146-150; Meanwell (EX1051), ¶¶80-85, 109; *supra* pp.26-39; *see LG Elecs.*, 39 F.4th at 1373; *In re Yale*, 434 F.2d at 668.

As discussed previously, a POSA would have known, in aqueous media such as human plasma, the salt form of the diester epinephrine compounds would rapidly dissociate into their corresponding non-salt (*i.e.*, free-base) forms and acid radicals. *Supra*, pp.39-41. Accordingly, Table 3's disclosure of the salt-forms of the identified diester epinephrine compounds also taught the corresponding non-salt forms of those compounds. Rautio (EX1050), ¶¶114, 135-137, 139-140, 146-147, 171-172, 290-300, 332; Meanwell (EX051); ¶¶77-79, 108, 111; *supra* pp.39-41. Finally a POSA would have recognized that Table 3 of Truelove 1 discloses the skeletal structures of the correctly named non-salt diester epinephrine compounds recited in Claim 2 where both R substituents are CH<sub>3</sub> (*i.e.*, diacetoxy)

and CH<sub>2</sub>CH<sub>3</sub> (*i.e.*, dipropionoxy). Rautio (EX1050), ¶¶138-151, 178-179; Meanwell (EX1051), ¶¶35, n.5, 80-82, 90, 109; *supra* pp.26-39.

*[ii] “wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration”*

*See, e.g.*, Ground 1, Section XI(A)(1)[i], *supra* pp.48.

*[iii] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

*See, e.g.*, Ground 1, Section XI(A)(1)[iv], *supra* p.50.

*[iv] “and has a half-life  $t_{1/2}$  range from 1-6 minutes.”*

A POSA would have corrected the obvious nomenclature errors in Truelove 1, and recognized that Table 3 actually discloses (i) L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, and (ii) L-3,4-dipropionoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, which in an aqueous media would rapidly dissociate into their corresponding free-base or non-salt forms (i) L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol; and (ii) L-3,4-dipropionoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol. Rautio (EX1050), ¶¶139, 144-146, 150-151; Meanwell (EX1051), ¶¶77-81, 83, 85; *supra* pp.26-41. Consequently, a POSA would have recognized that, once administered sublingually or buccally, the salt forms, as well as their corresponding non-salt or

free-base forms, would be considered equivalent in terms of the ability to reform into the parent epinephrine compound. Rautio (EX1050), ¶¶135-136, 297-298; Meanwell (EX1051), ¶¶77-79, 83, 85, 108-109, 111. As a result, the half-life  $t_{1/2}$  values of the salt forms of the diester epinephrine compounds disclosed in Table 3 would be essentially the same as their corresponding non-salt or base-base forms. Thus, a POSA would have understood that Table 3 discloses the half-life  $t_{1/2}$  values of L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and L-3,4-dipropionoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol are 3 and 4 minutes, respectfully. Rautio (EX1050), ¶¶135-150, 296-300, 331-343; Meanwell (EX1051), ¶¶77-79, 83, 85, 109; *supra* pp.31-41.

The diester epinephrine compounds recited in claim 2 would have been obvious under 35 U.S.C. § 103 based on Truelove 1, Ashraf, and the Almoazen Paper. Rautio (EX1050), ¶¶6(A), 288-300, 308-310, 315-316, 330-343.

### 3. Claim 3

*[i] “The compound of claim 2, wherein the compound is selected from the group consisting of 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate; 4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-*

*methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate;”*

The compounds identified in Table 3 of Truelove 1 are misnamed, actually disclose (i) L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, and (ii) L-3,4-dipropionoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, and also teach the corresponding free-base or non-salt forms of these compounds: (i) L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol, and (ii) L-3,4-dipropionyl- $\alpha$ -[(methylamino)-methyl]benzyl alcohol. *Supra* pp.31-33. A POSA would have recognized that, using an alternative but equally acceptable naming convention, the equivalent names of the free-base forms of these diester epinephrine compounds are (i) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **diacetate** and (ii) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**.<sup>16</sup> Rautio (EX1050), ¶¶139, 143-146, 149-151, 178-179, 349-351, 355-356; Meanwell (EX1051), ¶¶80-81, 83, 85, 109. *Supra* pp.31-41.

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<sup>16</sup> This compound is alternatively known as “4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropanoate**.” *Supra* pp.12-13, 37.

*[ii] “and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient,”*

Truelove 1 discloses a host of “pharmaceutically acceptable carriers.”

EX1002, 6:34-59. Additionally, the Almoazen Paper teaches that epinephrine can be combined with excipients. EX1022, p.0013. Finally, Ashraf discloses use of “excipient carrier particles” with sublingual tablets. EX1003, p.36; *see* Rautio (EX1050), ¶¶124, 181, 191, 193.

*[iii] “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.”*

*See, e.g.,* Ground 1, Section XI(A)(1)[iv], *supra* p.50.

Claim 3 would have been obvious under 35 U.S.C. § 103 in view of Truelove 1, Ashraf, and the Almoazen Paper. Rautio (EX1050), ¶¶6(A), 345-358, 416.

**B. Ground 2: Truelove 3, Ashraf, Almoazen Paper [Claims 1-3]**

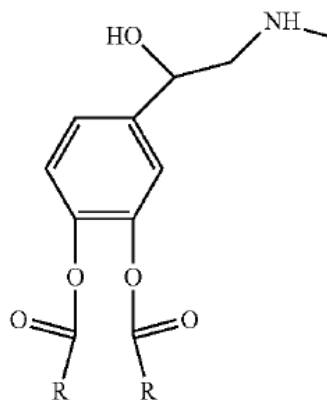
The arguments in support of Ground 1 and the disclosures of Truelove 1, Ashraf, and the Almoazen Paper are incorporated herein. *Supra* pp.48-57.

**1. Claim 1**

*[i] “A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration”*

*See, e.g.,* Ground 1, Section XI(A)(1)[i], *supra* pp.48. Truelove 3 also describes diester isoproterenol compounds that can be administered using “buccal patches.” EX1008, 7:35-40; *supra* p.44-46.

*[ii] “of a Formula:*



*wherein R is selected from the group consisting of . . . -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> . . . or a pharmaceutically acceptable salt thereof,”*

Table 3 of Truelove 3 discloses 3,4-dibutyroxy-α-[(isopropylamino)]-methylbenzyl alcohol hydrochloride. EX1008, 10:67-68. “Dibutyroxy” signifies

that the R substituents of both ester promoieties are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. Rautio (EX1050), ¶¶208, 365.

Not only are isoproterenol and epinephrine structurally similar, but the same hydroxy groups on these catechols are often modified by attaching the same ester promoieties. *Supra* pp.44-46. Because of this close structural similarity, a POSA would have expected that Truelove 3's disclosure of the diester isoproterenol compound where the R substituents of both ester promoieties are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> (*i.e.*, 3,4-dibutyroxy- $\alpha$ -[(isopropylamino)]-methyl]benzyl alcohol) taught the diester epinephrine compound having promoieties with the same R substituents (*i.e.*, L-3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol). Rautio (EX1050), ¶¶203, 206-216. Accordingly, Truelove 3 teaches the structure recited in challenged claim 1 where both R substituents are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. EX1050, ¶¶203, 205-214.

*[iii] “wherein said compound has a log P value in the range of about 0.5-6.0”*

*See, e.g.,* Ground 1, Section XI(A)(1)[iii], *supra* pp.50.

*[iv] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

*See, e.g.,* Ground 1, Section XI(A)(1)[iv], *supra* p.50.

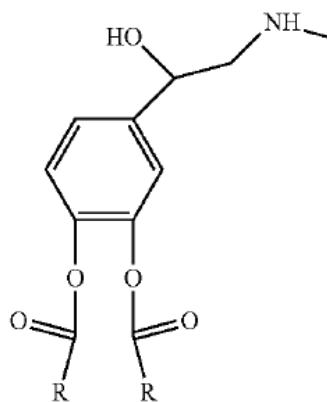
[v] “and has a half-life range from 1-6 minutes.”

Table 3 of Truelove 3 discloses that the diester isoproterenol compound, where both R substituents of the ester promoieties are  $\text{CH}_2\text{CH}_2\text{CH}_3$  has a 6 minute half-life  $t_{1/2}$ . EX1008, 10:68-69. Given the close structural similarity between isoproterenol and epinephrine, a POSA would have expected a diester epinephrine compound with the same ester promoieties would have the same 6 minute half-life  $t_{1/2}$ . Rautio (EX1050), ¶¶216-214.

Claim 1 would have been obvious under 35 U.S.C. § 103 in view of the teachings of Truelove 3 Ashraf, and the Almoazen Paper. EX1050, ¶¶6(B), 359-373, 416.

## 2. Claim 2

[i] “A compound of a Formula



*wherein R is selected from the group consisting of:*

*CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub> and . . . ”*

Table 3 of Truelove 3 discloses the diester isoproterenol compounds (i) 3,4-diacetoxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol hydrochloride and (ii) 3,4-dipropionyxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol hydrochloride.

EX1008, 10:60-68. The terms “diacetoxy” and “dipropionyxy” signify that the R substituents of the ester promoieties of these compounds are CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub>, respectively. Rautio (EX1050), ¶¶208, 377-384.

Table 3 discloses the salt forms of these diester isoproterenol compounds. However, a POSA would have known, in an aqueous media, the salt forms of these isoproterenol compounds would rapidly dissociate into the compounds' corresponding free-base or non-salt forms. EX1050, ¶¶135-137, 203-216, 293-297, 376-384. Accordingly, a POSA would have known that Truelove 3's disclosure of (i) 3,4-diacetoxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol hydrochloride and (ii) 3,4-dipropionyxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol hydrochloride, also taught the corresponding free-base or non-salt form of (i) 3,4-diacetoxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol and (ii) 3,4-dipropionyxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol, respectively. EX1050,

*id.* Additionally, given the close structural similarity between isoproterenol and epinephrine, a POSA would have anticipated that Truelove 3's disclosure of diester isoproterenol compounds where the R substituents of the ester promoieties are CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub> also taught diester epinephrine compounds with the same R substituents (*i.e.*, L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and L-3,4-dipropionyxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol). Rautio (EX1050), ¶¶206-216, 382-389. *See supra* 39-41, 44-46.

Accordingly, Table 3 of Truelove 3 teaches the diester epinephrine compounds recited in claim 2 where the R substituents are CH<sub>3</sub> or CH<sub>2</sub>CH<sub>3</sub>. EX1050, ¶¶205-216, 379-384.

*[ii] “wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration”*

*See, e.g.*, Ground 1, Section XI(A)(1)[i], *supra* pp.48. Truelove 3 also teaches that diester isoproterenol compounds can be administered using “buccal patches.” EX1008, 7:35-49.

*[iii] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

*See, e.g.*, Ground 1, XI(A)(1)[iv], *supra* p.50

*[iv] “and has a half-life  $t_{1/2}$  range from 1-6 minutes.”*

A POSA would have known that the disclosure of the salt form of the diester isoproterenol compounds in Table 3 of Truelove 3 taught the corresponding free-base (*i.e.*, free-base) form of these compounds. Rautio (EX1050), ¶¶135,-136, 205-206, 379-387. Because of the close structural similarity between isoproterenol and epinephrine, a POSA would have expected that non-salt form of diester isoproterenol and epinephrine compounds having the same ester promoieties would have the same half-life  $t_{1/2}$  values. EX1050. Since the diester isoproterenol compounds, 3,4-diacetoxy- $\alpha$ -[(isopropylamino)]-methyl]benzyl alcohol and 3,4-dipropionyxy- $\alpha$ -[(isopropylamino)]-methyl]benzyl alcohol have half-life  $t_{1/2}$  values of 3 and 4 minutes, respectively, a POSA would have expected that diester epinephrine compounds with the same ester promoieties, L-3,4-diacetoxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol and L-3,4-dipropionyxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol, would also have half-life  $t_{1/2}$  values of 3 and 4 minutes, respectively. EX1050, ¶¶210-216.

Claim 2 would have been obvious under 35 U.S.C. § 103 in view of Truelove 3, Asraf, and the Almoazen Paper. EX1050, ¶¶6(B), 374-319, 416.

### 3. Claim 3

*[i] “The compound of claim 2, wherein the compound is selected from the group consisting of 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate;”*

Given the close structural similarity between isoproterenol and epinephrine, Table 3 of Truelove 3 teaches diester epinephrine compounds (i) 3,4-**diacetoxy**-α-[(methylamino)-methyl]benzyl alcohol hydrochloride and (ii) 3,4-**dipropionoxy**-α-[(methylamino)-methyl]benzyl alcohol hydrochloride). EX1050, ¶¶204, 206-216, 380-385. A POSA would have known, using an alternative, but an equally acceptable naming convention, these diester epinephrine compounds could also be named (i) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **diacetate** and (ii) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**<sup>17</sup>, respectively. Rautio (EX1050), ¶¶208, 381-384. Meanwell (EX1051), ¶¶80-81, 109.

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<sup>17</sup> This compound can also be referred to as “4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**.” *Supra* pp.12-13, 37.

Accordingly, Truelove 3 discloses the compounds named in claim 3. Rautio (EX1050), ¶¶379-399.

*[ii] “and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient,”*

*See, e.g.,* Ground 1, XI(A)(3)[ii], *supra* p.57. Truelove 3 also discloses a host of “pharmaceutically acceptable carriers.” EX1008 7:43-50.

*[iii] “wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.”*

*See, e.g.,* Ground 1, XI(A)(1)[iv], *supra* p.50.

Claim 3 would have been obvious under 35 U.S.C. § 103 in view of Truelove 3, Ashraf, and the Almoazen Paper. Rautio (EX1050), ¶¶6B, 392-402, 416.

**C. Ground 3: Truelove 1, Truelove 3, Ashraf, Almoazen Paper, Fuchs, Schobel, Florence [Claims 1-3]**

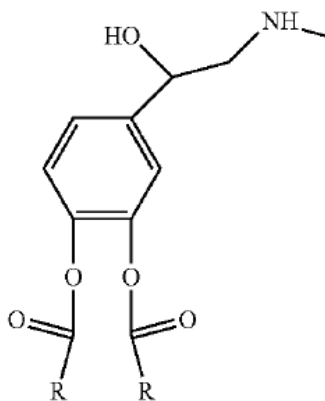
The arguments in support of Grounds 1-2, and the teachings of Truelove 1, Truelove 3, Ashraf, and the Almoazen Paper are incorporated herein. *Supra* pp.48-65.

**1. Claim 1**

*[i] “A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration”*

*See, e.g.*, Ground 1, Section XI(A)(1)[i], *supra* pp.48. Additionally, Truelove 3 teaches structurally similar catechols can be administered using “buccal patches.” EX1008, 7:35-40. *Supra* p.44-46. Further, Schobel describes films designed for administration of epinephrine and salts and esters thereof, *i.e.* epinephrine prodrugs, to human mucosa. *See, e.g.*, EX1021, 1:26-46; 13:15-14:19; 15:55-65; 45:19-20; 46:45-59. *Supra* p.46-47. Finally, Fuchs discloses the use of films for the administration of drugs to the mucosal membranes of the body. EX1004, 2:28-38; *see* Rautio (EX1050), ¶¶198-200.

*[ii] “of a Formula:*



*wherein R is selected from the group consisting of . . . -  
CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> . . . or a pharmaceutically acceptable salt  
thereof,”*

As discussed in Ground 1, a POSA would have:

- recognized Truelove 1's obvious nomenclature error regarding the “dibutryl” compound identified in Table 3;
- disregarded Truelove 1's mistake;
- substituted the correct name (*i.e.*, L-3,4-**dibutyroxy**- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate) in its place; and
- understood the R substituents of this diester epinephrine compound are **CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>**.

*Supra* p.48-50.

As detailed in Ground 2, given isoproterenol's and epinephrine's close structural similarity, a POSA would have expected that Truelove 3's disclosure of the diester isoproterenol compound where the R substituents of both ester promoieties are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> taught the diester epinephrine compound having the same ester promoieties. *Supra* p.58-59.

Accordingly, both Truelove 1 and Truelove 3 teach the structure recited in challenged claim 1 where both R substituents are CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>. *See, e.g.*, Rautio (EX1050), ¶¶170-179, 205-210, 216, 319-322.

*[iii] “wherein said compound has a log P value in the range of about 0.5-6.0”*

*See, e.g.*, Ground 1, Section XI(A)(1)[iii], *supra* p.50. Florence also teaches the ideal log P values for buccal absorption typically falls within the range of 3.52 to 5.52. EX1015, Table 9.1, p.334. *Supra* p.46.

*[iv] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

*See, e.g.*, Ground 1, Section XI(A)(1)[iv], *supra* p.50. Schobel also teaches the methods and use of making oral rapidly dissolving films containing epinephrine compositions, including prodrugs *See, e.g.*, EX1021, 1:26-45, 13:37-67, 13:15-67; 14:13-18, 15:55-65; 16:57-27:2, ;45:19-20. *Supra* pp.46-47.

*[v] “and has a half-life range from 1-6 minutes.”*

Ground 1 demonstrated that a POSA would have understood that, despite Truelove 1’s nomenclature error, Table 3 actually discloses L-3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, that the R substituents of

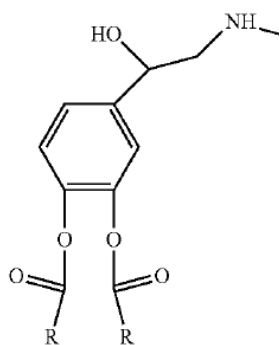
this compound's ester promoieties are  $\text{CH}_2\text{CH}_2\text{CH}_3$ , and that this diester epinephrine compound has a half-life  $t_{1/2}$  of 6 minutes. *Supra* pp.48-51.

Additionally, Table 3 of Truelove 3 discloses that the diester isoproterenol compound where both R substituents of the ester promoieties are  $\text{CH}_2\text{CH}_2\text{CH}_3$  has a half-life  $t_{1/2}$  of 6 minutes. EX1008, 10:68-69. As detailed in Ground 2, given the close structural similarity between isoproterenol and epinephrine, a POSA would have expected that a diester isoproterenol and epinephrine compounds with the same ester promoieties with the same R substituents (*i.e.*,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ) would have the same 6 minute half-life  $t_{1/2}$ . *Supra* pp.58-60.

The teachings of Truelove 1, Truelove 3, Ashraf, the Almoazen Paper, Fuchs, Schobel, and Florence render claim 1 obvious under 35 U.S.C. § 103. Rautio (EX1050), ¶¶6(C), 367-372, 387-388, 391, 403-406, 409-410, 412-413, 417.

## 2. Claim 2

[i] “A compound of a Formula:



wherein *R* is selected from the group consisting of:  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$  and . . .”

As discussed in Ground 1, a POSA would have understood that Truelove 1’s disclosure of the salt-forms of the correctly named diester epinephrine compounds in Table 3 taught the corresponding free-base or non-salt forms of these diester compounds. *Supra* pp.51-55. A POSA would have also recognized that the skeletal structures of both correctly named diester epinephrine compounds correspond to the structure recited in claim 2 where both *R* substituents are  $\text{CH}_3$  and  $\text{CH}_2\text{CH}_3$ . *Id.*

As detailed in Ground 2, in view of isoproterenol’s and epinephrine’s close structural similarity, a POSA would have expected that Truelove 3’s disclosure of diester isoproterenol compounds where the *R* substituents of both ester promoieties are (i)  $\text{CH}_3$  and (ii)  $\text{CH}_2\text{CH}_3$  taught diester epinephrine compounds with the same

R substituents (*i.e.*, (i) L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and (ii) L-3,4-dipropionyloxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol). *Supra* pp.60-63.

Truelove 1 and Truelove 3 each disclose the compounds depicted in claim 2 where the R substituents of both ester promoieties are CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub>. *See, e.g.*, Rautio (EX1050), ¶¶138-152, 208-209, 216, 335-336, 379-389.

*[ii] “wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration”*

Truelove 1, the Almoazen Paper, Truelove 3 and Schobel satisfy this limitation. EX1002, 6:29-32; EX1022, pp.1012-13, 1015; EX1021, 5:8-13; 6:41-43. *Supra* p.46-47.

*[iii] “and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film”*

*See, e.g.*, Ground 1, Section XI(A)(1)[iv], *supra* p.50. Schobel also satisfies this limitation. EX1022, pp.1012-13, 1015; EX1021, 1:17-46; 6:41-43; 45:19-20. *Supra* p.46-47.

*[iv] “and has a half-life  $t_{1/2}$  range from 1-6 minutes.”*

As discussed in Ground 1, a POSA would have understood that Table 3 of Truelove 1 teaches L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and

L-3,4-dipropiony- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and reports that the half-life  $t_{1/2}$  values of these diester epinephrine compounds are 3 and 4 minutes, respectfully. *Supra* pp.51-55.

Additionally, as discussed in Ground 2, given the close structural similarity of isoproterenol and epinephrine, a POSA would have expected that isoproterenol and epinephrine compounds with the same ester promoieties would have the same half-life  $t_{1/2}$  values. *Supra* p.60-63. Thus, a POSA would have expected the diester isoproterenol compounds, 3,4-diacetoxy- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol and 3,4-dipropiony- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol and the diester epinephrine compounds with the same ester promoieties, L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol and L-3,4-dipropiony- $\alpha$ -[(methylamino)-methyl]benzyl alcohol, would have the same half-life  $t_{1/2}$  values of 3 and 4 minutes, respectively. EX1050, ¶¶210-216.

Claim 2 would have been obvious under 35 U.S.C. § 103 in view of Truelove 1, Truelove 3, Ashraf, the Almoazen Paper, Fuchs, Schobel, and Florence. Rautio (EX1050), ¶¶6(C), 374-391, 417.

### 3. Claim 3

*[i] “The compound of claim 2, wherein the compound is selected from the group consisting of 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate;”*

A POSA would have recognized that using an alternative naming convention, L-3,4-**diacetox**y- $\alpha$ -[(methylamino)methyl]benzyl alcohol and L-3,4-**dipropionox**y- $\alpha$ -[(methylamino)-methyl]benzyl alcohol taught by Truelove 1 and 3 could also be called 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **diacetate** and 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**,<sup>18</sup> respectively. Rautio (EX1050), ¶¶136-151, 178-179, 333-341, 349-351, 355-358; Meanwell (EX1051), ¶¶80-81, 109.

*[ii] “and a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient,”*

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<sup>18</sup> This compound can also be identified as “4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropanoate**.” *Supra* pp.12-13, 37.

*See, e.g.*, Ground 1, XI(A)(3)[ii], *supra* p.55-57. Truelove 3 also describes a host of “pharmaceutically acceptable carriers.” EX1008, 7:43-50.

[iii] “*wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.*”

*See, e.g.*, Ground 1, XI(A)(1)[iv], *supra* p.50.

Claim 3 would have been obvious under 35 U.S.C. § 103 in view of Truelove 1, Truelove 3, Ashraf, the Almoazen Paper, Fuchs, Schobel, and Florence. Rautio (EX1050), ¶¶6(C), 403-413, 417.

## **XII. Motivation to Combine**

### **A. Ground 1: Truelove 1, Ashraf, and Almoazen Paper**

A POSA would have possessed reasons and motivation to combine the teachings of Truelove 1, Ashraf, and the Almoazen Paper because each relate to the same field of endeavor (*i.e.*, the buccal administration of drug formulations), and would have had a reasonable expectation of obtaining the diester epinephrine compounds having half-life  $t_{1/2}$  values of 1-6 minutes as recited in claims 1-3 of the ‘437 patent. *See, e.g.*, Rautio (EX1050), ¶¶288-300, 305-306, 308-310, 315-316, 318-358.

It was known that epinephrine should be administered promptly after conditions such as anaphylaxis are suspected. *See, e.g.*, EX1029, pp.477-78; 480.e10. As an alternative to intramuscular injection, a POSA would have recognized that the Almoazen Paper describes the administration of unit doses of epinephrine to the buccal cavity using rapidly dissolving films. EX1022, pp.1012-13. Additionally, a POSA would have been aware Truelove 1 teaches the use of buccal patches to administer a diester epinephrine compound. EX1002, 6:29-32. *See, e.g., supra* pp. 24-25.

A POSA would have also appreciated that the Log P value is of great importance when delivering drugs through a mucosal layer. Rautio (EX1050), ¶¶305-307. Therefore, a POSA would have considered references such as Ashraf and its teaching that the acceptable Log P range for sublingual and/or buccal administration is about 1-6. EX1003, Table II, p.35; see EX1001, 7:11-18. In fact, the '437 patent admits that Ashraf discloses Log P values of 0.5-6.0. EX1001, 5:7-30.

Given the importance of administering epinephrine rapidly, a POSA would have also considered disclosures such as Truelove 1 to confirm the types of ester promoieties that, after passage through the oral mucosal layer, would rapidly

cleave and release epinephrine. *See, e.g.*, EX1002, 9:26-37; Rautio (EX1050),

¶¶290-293, 308-309. However, a POSA reviewing Truelove 1 would have:

- recognized that the compounds identified in Table 3 were misnamed as ketone derivatives;
- disregarded Table 3's nomenclature errors;
- substituted in their place the correct names of the disclosed diester compounds (*i.e.*, (i) L-3,4-dibutyroxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, (ii) L-3,4-diacetoxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate, (iii) L-3,4-dipropionyloxy- $\alpha$ -[(methylamino)-methyl]benzyl alcohol hydroperchlorate);
- recognized that the R substituents of the ester promoieties of these compounds are (i) CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, (ii) CH<sub>3</sub> and (iii) CH<sub>2</sub>CH<sub>3</sub>;
- expected that upon dissolution in human plasma, the half-life  $t_{1/2}$  values of the salt and non-salt (*i.e.*, free-base) forms of these compounds would have been the same; and

- understood, based on Table 3's disclosure, that the respective half-life  $t_{1/2}$  values of these diester epinephrine compounds were (i) 6 minutes, (ii) 3 minutes, and (iii) 4 minutes, respectively.

*See, e.g.*, Rautio (EX1050), ¶¶128-134, 138-152, 170-179; Meanwell (EX1051), ¶¶79-82, 84, 90-91, 109; *supra* pp.26-41.

A POSA would have been motivated to combine Truelove 1's disclosure of diester epinephrine compounds with half-life  $t_{1/2}$  values of 1-6 minutes, Ashraf's teaching of acceptable Log P values for buccal or sublingual administration, and the Almoazen Paper's disclosure of buccal administration of epinephrine in unit dosage forms via rapidly dissolving films, and without undue experimentation, would have had more than a reasonable expectation of success of obtaining the diester epinephrine compounds recited in challenged claims 1 and 2 where the R substituents of the ester promoieties are  $\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_3$  and  $\text{CH}_2\text{CH}_3$ , and where the compounds' half-life  $t_{1/2}$  values range from 1-6 minutes. Rautio (EX1050), ¶¶288-294, 305-310, 315-316, 318-343.

Accordingly, claims 1-2 of the '437 patent would have been obvious based on the teachings of Truelove 1, Ashraf, and the Almoazen Paper. EX1050, ¶¶318-343.

Claim 3 specifically recites the names of the diester epinephrine compounds depicted by claim 2 where both R substituents of the ester promoieties are CH<sub>3</sub> and CH<sub>2</sub>CH<sub>3</sub> and requiring pharmaceutically acceptable carriers or excipients. A POSA would have recognized that both the Almoazen Paper, and Ashraf disclose the use of carriers and excipients. *See, e.g.*, EX1022, p.1013; EX1003, p.36. A POSA would have also known that the diester epinephrine compounds disclosed in Table 3 (i) 3,4-**diacetoxy**- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol, and (ii) 3,4-**dipropionoxy**- $\alpha$ -[(isopropylamino)-methyl]benzyl alcohol), using different, but equally acceptable nomenclature, could be named (i) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **di-acetate** and (ii) 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene **dipropionate**. Rautio (EX1050), ¶¶344-358; Meanwell (EX1051), ¶¶80-81, 83, 85, 109.

In sum, a POSA not only could have made but would have also been motivated to combine the teachings of Truelove 1, Ashraf, and the Almoazen Paper, and these teachings would have provided a POSA with a reasonable expectation of arriving at the diester epinephrine compounds recited in challenged claims 1-3 without undue experimentation. Rautio (EX1050), ¶¶6(A), 318-358, 415.

**B. Ground 2: Truelove 3, Ashraf, and Almoazen Paper**

The discussion regarding the unpatentability of claims 1-3 based on Ground 1, and the teachings of Truelove 1, Ashraf, and the Almoazen Paper are incorporated herein. *Supra* pp.74-78.

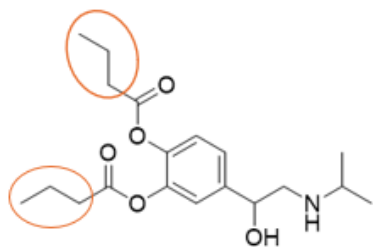
A POSA would have also motivated to combine Truelove 3, Ashraf, and the Almoazen Paper because each relates to the same field of endeavor (*i.e.*, the buccal administration of drug formulations), and would have had a reasonable expectation of arriving at the diester epinephrine compounds with half-life  $t_{1/2}$  values as recited in claims 1-3 of the '437 patent. Rautio (EX1050), ¶¶288-300, 305-306, 308-310, 359-402.

Given the importance of administering epinephrine rapidly, a POSA would have also considered references disclosing prodrug compounds that are structurally similar to epinephrine to ascertain promoieties that would rapidly cleave and liberate epinephrine in a relatively short period of time, (*i.e.*, half-life  $t_{1/2}$ ). EX1050, ¶¶211-216, 292. Accordingly, a POSA would have recognized that Truelove 3 teaches diester isoproterenol compounds with half-life  $t_{1/2}$  values of 1-6 minutes. EX1008, 10:59-70. Based on the close structural similarity between isoproterenol and epinephrine, a POSA seeking to synthesize epinephrine compounds with a

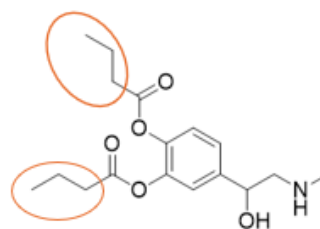
rapid half-life  $t_{1/2}$  (e.g., 1-6 minutes) would have been motivated by the teachings of Truelove 3 to synthesize diester epinephrine compounds using the same ester promoieties disclosed in Truelove 3. Rautio (EX1050), ¶¶211-216, 365-369, 381-389.

Further, although Table 3 of Truelove 3 discloses the salt-forms of these diester isoproterenol compounds, a POSA would have understood that the salt form of a prodrug would dissociate into corresponding non-salt (*i.e.*, free-base) form and acid ions before reaching the plasma and that both the salt and non-salt forms of these compounds would have the same half-life  $t_{1/2}$ . EX1050, ¶¶208, 366.

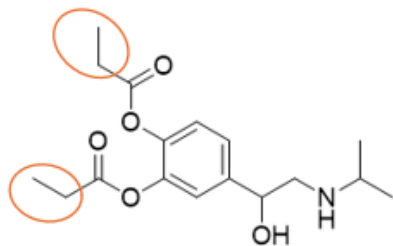
Consequently, because of (a) isoproterenol's and epinephrine's close structural similarity, and (b) the same ester promoieties substituents (*i.e.*,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ) on the same locations of the benzene ring, a POSA would have expected the half-life  $t_{1/2}$  values of diester isoproterenol compounds disclosed in Truelove 3 and the diester epinephrine compounds recited in challenged claims 1-3 would also range from 1-6 minutes. Rautio (EX1050), ¶¶206-216, 364-369.



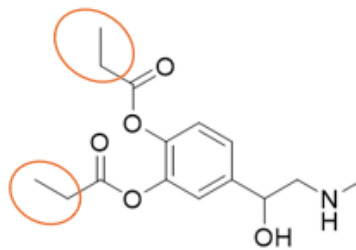
Truelove 3, Table 3  
 3,4-dibutyroxy- $\alpha$ -((isopropylamino)-  
 methyl)benzyl alcohol  
 Promoiety Substitute =  $-\text{CH}_2\text{CH}_2\text{CH}_3$   
 $t_{1/2}$  = 360 seconds = 6 minutes



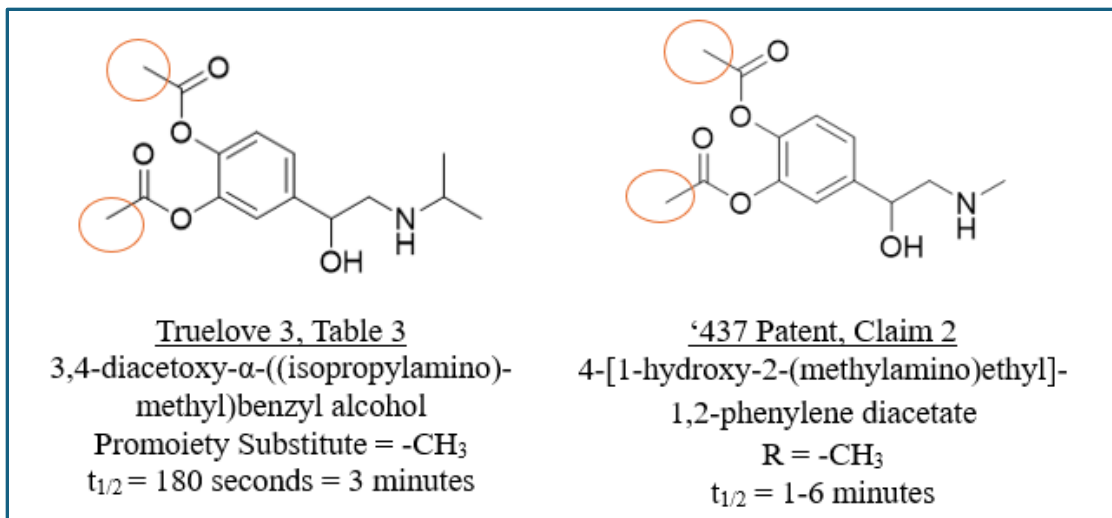
'437 Patent, Claim 1  
 4-(1-hydroxy-2-(methylamino) ethyl)-  
 1,2-phenylene dibutyrate  
 $\text{R} = -\text{CH}_2\text{CH}_2\text{CH}_3$   
 $t_{1/2}$  = 1-6 minutes



Truelove 3, Table 3  
 3,4-dipropionoxy- $\alpha$ -((isopropylamino)-  
 methyl)benzyl alcohol  
 Promoiety Substitute =  $-\text{CH}_2\text{CH}_3$   
 $t_{1/2}$  = 240 seconds = 4 minutes



'437 Patent, Claim 2  
 4-[1-hydroxy-2-(methylamino)ethyl]-  
 1,2-phenylene dipropionate  
 $\text{R} = -\text{CH}_2\text{CH}_3$   
 $t_{1/2}$  = 1-6 minutes



EX1050, ¶¶365, 383-384.

In view of the disclosure and teachings of Truelove 3, a POSA would have had a reasonable likelihood of success, without undue experimentation of obtaining the diester epinephrine compounds having half-life  $t_{1/2}$  values of 1-6 minutes as recited in challenged claims 1-3. EX1050, ¶¶206-216, 360-391.

A POSA would have also recognized that the diester compounds taught by Truelove 3 could be named using alternate naming conventions as recited in claim 3. EX1050, ¶¶208-209; *see also supra* p.12-13.

Additionally, as detailed in Ground 1, a POSA would have also considered references such as Ashraf and its teaching of the acceptable Log P values for sublingual and/or buccal administration. *Supra* pp.42-43, 50. Further, a POSA would have recognized the Almoazen Paper describes the administration of unit

doses of epinephrine to the buccal cavity using rapidly dissolving films. A POSA would have also considered Truelove 3, which discloses the use of buccal patches to administer diester epinephrine compounds. *Supra* p.44-46.

A POSA not only could have made but would have been motivated to make the combinations and/or modifications to Truelove 3, Ashraf, and the Almoazen Paper, and the teachings of these references would have provided a POSA a reasonable expectation of arriving at the compounds recited in challenged claims 1-3 without undue experimentation. Rautio (EX1050), ¶¶6(B), 359, 402, 416.

**C. Ground 3: Truelove 1, Truelove 3, Ashraf, Almoazen Paper, Fuchs, Schobel, and Florence**

The discussion regarding the unpatentability of claims 1-3 based on Grounds 1 and 2, and the teachings of Truelove 1, Truelove 3, Ashraf, and the Almoazen Paper are incorporated herein. *Supra* pp.74-83.

A POSA seeking to develop epinephrine prodrugs with rapid half-life  $t_{1/2}$  values that could be administered sublingually or buccally would have considered disclosures relating to the ester moieties used to synthesize prodrugs, their associated half-life values and the salt form of those prodrugs, as disclosed in Truelove 1 and Truelove 3, and would have had a reasonable expectation of

obtaining diester epinephrine compounds that could penetrate the oral mucosa and have the same half-life  $t_{1/2}$  values of 1-6 minutes. Rautio (EX1050), ¶¶318-402.

A POSA would have been aware that Florence discloses the ideal Log P values for buccal absorption is typically 3.52-5.52. EX1015, p.334. A POSA would have also known references such as Fuchs and Schobel teach films designed for mucosal drug administration. Rautio (EX1050), ¶¶198-200, 234-239. For example, Fuchs describe “unit dosage forms” adapted for administration to body cavities. EX1004, 2:33-38; *see* EX1001, 2:39-47 (Fuchs discloses “[f]ilms that incorporate a pharmaceutically active ingredient” that can be administered to “mucosal membrane areas of the body”). Schobel describes rapidly dissolving film used for oral administration of epinephrine compounds, including epinephrine prodrugs. EX1021, 1:36-45, 13:37-67, 14:13-18, 15:62-65, 45:19-20; *see id.*, 16:57-27.2.

A POSA not only could have made but would have been motivated to make the combinations and/or modifications to Truelove 1, Truelove 3, Ashraf, the Almoazen Paper, Fuchs, Schobel, and Florence, as detailed previously, and the teachings of these references would have provided a POSA a reasonable

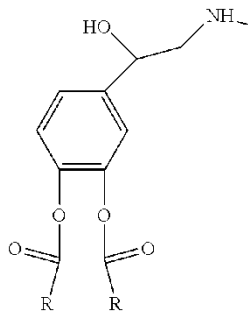
expectation of arriving at the compounds recited in challenged claims 1-3 without undue experimentation. Rautio (EX1050), ¶¶6(C), 403-413, 417.

**XIV. CLAIM CHART**

In the following claim chart, the following shorthand is used: first the ground number, *e.g.*, G1 stands for Ground 1; then the ‘437 Patent claim number, followed by the claim limitation, *e.g.*, 1A stands for claim 1’s first claim limitation. Thus, G1-1A stands for Ground 1 – Claim 1, first (A) claim limitation.

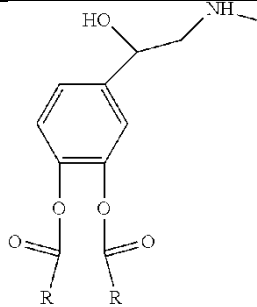
**GROUND 1**

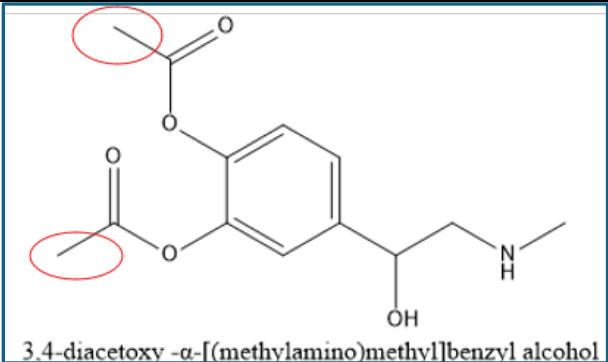
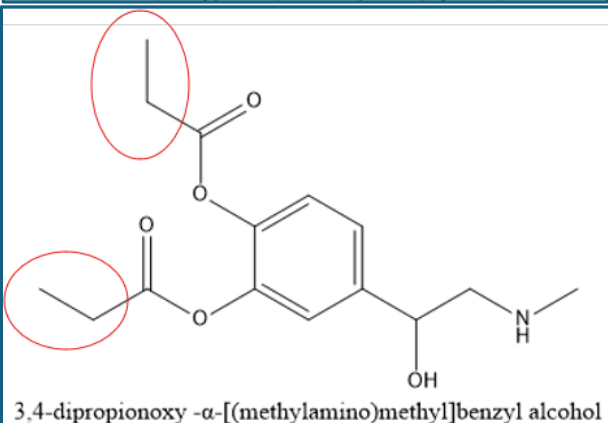
| <b>GROUND 1</b><br><b>Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                           | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <u>Claim 1.</u><br><br>[G1-1A]<br>A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration | <p><b>Truelove 1 (EX1002)</b><br/>           “[T]he new compound and its non-toxic salts are administered in the form of . . . buccal patches. . . .” (EX1002, 6:29-32.)</p> <p><b>Almoazen Paper (EX1022)</b><br/> <i>“Objective:</i> To develop a fast dissolving film [“FDF”] strip containing epinephrine HCl for the potential treatment of pediatric anaphylaxis.” (EX1022, Abstract, p.1012.)</p> <p>“Fast dissolving films (FDF) . . . are very thin strips that disintegrate or dissolve very rapidly in the oral cavity releasing the medication to be absorbed through the oromucosal route.” (EX1022, p.1012.)</p> <p>“The formulations compositions of the FDFs are mentioned in <b>Table 1.</b>” (EX1022, p.1013, emphasis added.)</p> |

| GROUND 1                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|--|--|----------|-----------------------------------------|--|--|-------|--------|-------|----------------------------------------------------------------------------------|----|----|-----|------------------------------------------------------------------------------------|----|----|-----|-----------------------------------------------------------------------------------|-----|-----|-----|-----------------------------------------------------------------------------------|-----|-----|-------|
| Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| CLAIMS<br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                 | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| <p>[G1-1B]<br/>of a Formula:</p> <div></div> <p>wherein R is selected from the group consisting of: —<br/>***<br/>-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,<br/>***<br/>or a pharmaceutically acceptable salt thereof,</p> | <p><b>Ashraf (EX1003)</b></p> <p>Ashraf discloses pharmaceutically acceptable carriers and excipients for its oral mucosa drugs. (EX1003, p.36.)</p> <p>*****</p> <p><b>Truelove 1 (EX1002)</b></p> <p>Truelove 1, Table 3, EX1002, 9:26-38, copied below,</p> <table><tr><th colspan="4">TABLE 3</th></tr><tr><th rowspan="2">Compound</th><th colspan="3">Rate of hydrolysis in <math>t_{1/2}</math> seconds</th></tr><tr><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>L-3,4-diacetyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>20</td><td>45</td><td>180</td></tr><tr><td>L-3,4-dipropionyl-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol hydroperchlorate</td><td>50</td><td>90</td><td>240</td></tr><tr><td>L-3,4-dibutyryl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>100</td><td>160</td><td>360</td></tr><tr><td>L-3,4-dipivalyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>600</td><td>720</td><td>1,800</td></tr></table> <p>discloses “3,4-dibutyryl-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol hydroperchlorate”. A POSA would have recognized that as Truelove 1 was directed to and discloses diester derivatives of epinephrine, not the named ketone derivative, Truelove 1 was disclosing, as corrected, both (i) the salt “3,4-dibutyrylbutyroxy -<math>\alpha</math>-[(methylamino) methyl] benzyl alcohol hydroperchlorate” and (ii) the non-salt “3,4-dibutyrylbutyroxy-<math>\alpha</math>-[(methylamino) methyl] benzyl alcohol” compounds. The POSA would have further understood that “3,4-dibutyroxy-<math>\alpha</math>-[(methylamino) methyl] benzyl alcohol” discloses, as recited in claim 1, the compound with the following ChemDraw® generated compound structure and displayed compound name having the circled R</p> | TABLE 3 |       |  |  | Compound | Rate of hydrolysis in $t_{1/2}$ seconds |  |  | Horse | Rabbit | Human | L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 20 | 45 | 180 | L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydroperchlorate | 50 | 90 | 240 | L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 100 | 160 | 360 | L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 600 | 720 | 1,800 |
| TABLE 3                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| Compound                                                                                                                                                                                                                                                                                                        | Rate of hydrolysis in $t_{1/2}$ seconds                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
|                                                                                                                                                                                                                                                                                                                 | Horse                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Rabbit  | Human |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                                | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 45      | 180   |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                              | 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 90      | 240   |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                               | 100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 160     | 360   |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                               | 600                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 720     | 1,800 |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |

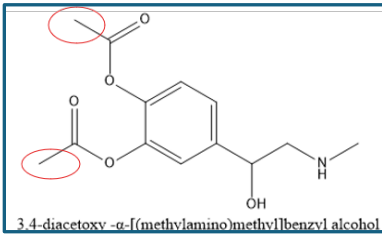
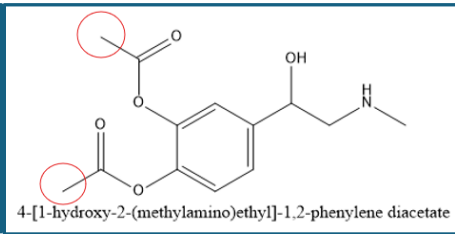
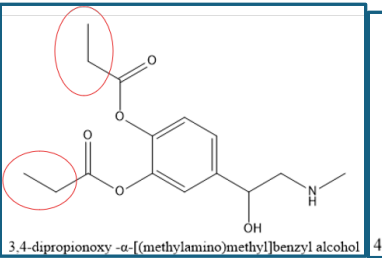
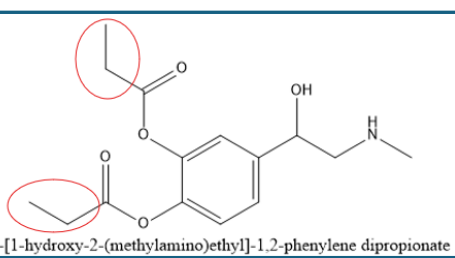
| GROUND 1                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| CLAIMS<br>[Ground # - Claim ID]                                                             | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                             | <p>substituent Group <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math> which POSA would have substantially the same, if not identical half-life <math>t_{1/2}</math> of <b>360 seconds or 6 minutes</b> as disclosed in Table 3.</p> <div data-bbox="618 625 1398 1077"> <p>3,4-dibutyroxy-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p> </div> <p>*****</p> <p><b>Ashraf (EX1003)</b></p> <p>“Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of <b>log P</b> (octanol/water partition coefficient) <b>values of 1 to 5.</b>” (EX1003, p.35, 2nd col., emphasis added).</p> <p>The inherent Log P of the claim 1 epinephrine compound with ester promoiety <b>R = <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math></b> is +0.8. See, ‘437 Patent (EX1001), Table 1, 5:29.</p> |
| [G1-1C]<br>wherein said compound has a <b>Log P value in the range of about 0.5-6.0</b> and |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

| <b>GROUND 1</b>                                                                                                                                                                              |                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                                                                      |                                                                                                                                                                                                                               |
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                       | <b>REFERENCES</b>                                                                                                                                                                                                             |
| <p>[G1-1D]<br/>wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G1-1E]<br/>has a half-life <math>t_{1/2}</math> range from 1-6 minutes.</p> | <p>*****</p> <p><b>Truelove 1 (EX1002), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussion for [G1-1A] above.</p> <p>*****</p> <p><b>Truelove 1 (EX1002)</b></p> <p>See discussion in [G1-1B] above.</p> |
| <p><u>Claim 2.</u></p> <p>[G1-2A]<br/>A compound of a Formula</p>                                                                                                                            | <p><b>Truelove 1 (EX1002)</b></p> <p>Truelove 1, Table 3, EX1002, 9:26-38, copied below</p>                                                                                                                                   |

| GROUND 1                                                                                                                                                                                                                                                     |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------|--|--|--|----------|-----------------------------------------|--|--|-------|--------|-------|--------------------------------------------------------------------------------|----|----|-----|----------------------------------------------------------------------------------|----|----|-----|---------------------------------------------------------------------------------|-----|-----|-----|---------------------------------------------------------------------------------|-----|-----|-------|
| Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                                                                                                                             |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| CLAIMS<br>[Ground # - Claim ID]                                                                                                                                                                                                                              |                                         | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| <div></div> <p>wherein R is selected from the group consisting of: <b>CH<sub>3</sub></b>, <b>CH<sub>2</sub>CH<sub>3</sub></b> and <b>CH(CH<sub>3</sub>)<sub>2</sub></b></p> |                                         | <table><tr><th colspan="4">TABLE 3</th></tr><tr><th rowspan="2">Compound</th><th colspan="3">Rate of hydrolysis in <math>t_{1/2}</math> seconds</th></tr><tr><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>L-3,4-diacetyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydropchlorate</td><td>20</td><td>45</td><td>180</td></tr><tr><td>L-3,4-dipropionyl-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol hydropchlorate</td><td>50</td><td>90</td><td>240</td></tr><tr><td>L-3,4-dibutyryl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydropchlorate</td><td>100</td><td>160</td><td>360</td></tr><tr><td>L-3,4-dipivalyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydropchlorate</td><td>600</td><td>720</td><td>1,800</td></tr></table> |       | TABLE 3 |  |  |  | Compound | Rate of hydrolysis in $t_{1/2}$ seconds |  |  | Horse | Rabbit | Human | L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate | 20 | 45 | 180 | L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydropchlorate | 50 | 90 | 240 | L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate | 100 | 160 | 360 | L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate | 600 | 720 | 1,800 |
| TABLE 3                                                                                                                                                                                                                                                      |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| Compound                                                                                                                                                                                                                                                     | Rate of hydrolysis in $t_{1/2}$ seconds |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
|                                                                                                                                                                                                                                                              | Horse                                   | Rabbit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Human |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate                                                                                                                                                                               | 20                                      | 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 180   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydropchlorate                                                                                                                                                                             | 50                                      | 90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 240   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate                                                                                                                                                                              | 100                                     | 160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 360   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydropchlorate                                                                                                                                                                              | 600                                     | 720                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1,800 |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |
|                                                                                                                                                                                                                                                              |                                         | <p>discloses the salt form and thus the non-salt form of the following corrected named diester compounds, namely “3,4- <b>diacetyl</b> <b>acetox</b>y-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol” and “3,4- <b>dipropionyl</b> <b>propionox</b>y-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol”. A POSA would have understood these compounds to have the ChemDraw® structures and displayed name as shown below with R substituent Groups <b>-CH<sub>3</sub></b> and <b>-CH<sub>2</sub>CH<sub>3</sub></b>, as recited in [G1-2A] circled, and that Table 3 also discloses that these diester epinephrine prodrug compounds would have substantially the same, if not identical half-lives <math>t_{1/2}</math> of <b>3 minutes and 4 minutes</b>, respectively.</p>                |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                  |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |       |

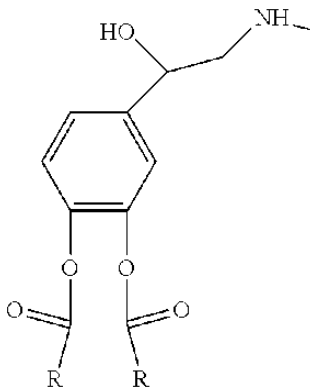
| <p style="text-align: center;"><b>GROUND 1</b></p> <p style="text-align: center;"><b>Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)</b></p>                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p style="text-align: center;"><b>CLAIMS</b></p> <p style="text-align: center;">[Ground # - Claim ID]</p>                                                                                                                                                                                          | <p style="text-align: center;"><b>REFERENCES</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p>[G1-2B]<br/>wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G1-2C]<br/>has a half-life <math>t_{1/2}</math> range from 1-6 minutes.</p> | <div style="text-align: center;">  <p>3,4-diacetoxy-α-[(methylamino)methyl]benzyl alcohol</p>  <p>3,4-dipropionyloxy-α-[(methylamino)methyl]benzyl alcohol</p> </div> <p style="text-align: center;">*****</p> <p><b>Truelove 1 (EX1002), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussed in [G1-1A] above for [G1-2B] disclosure.</p> |

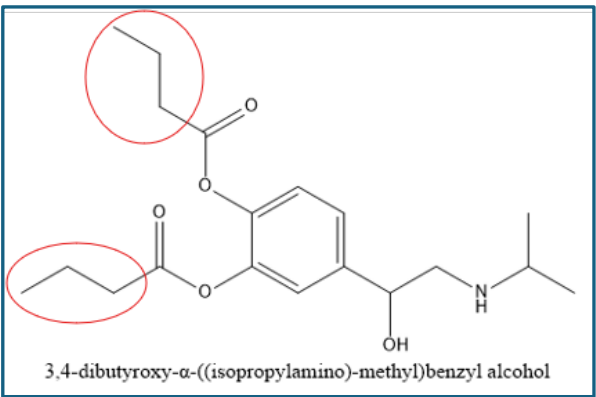
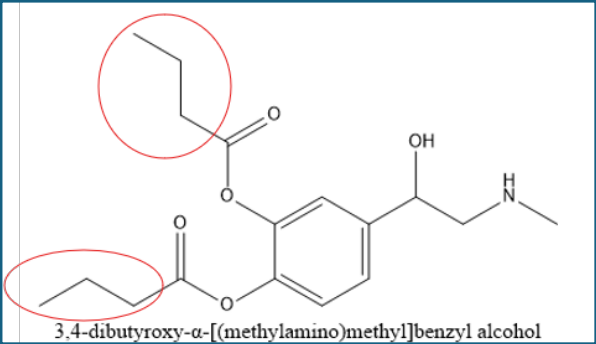
| GROUND 1                                                                                                                                                                                                                                                                                                  |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------|--|--|--|----------|-----------------------------------------|--|--|-------|--------|-------|----------------------------------------------------------------------------------|----|----|-----|------------------------------------------------------------------------------------|----|----|-----|-----------------------------------------------------------------------------------|-----|-----|-----|-----------------------------------------------------------------------------------|-----|-----|-------|
| Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                                                                                                                                                                          |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| CLAIMS<br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                           |                                         | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
|                                                                                                                                                                                                                                                                                                           |                                         | *****<br><b>Truelove 1 (EX1002)</b><br><br>See discussion in [G1-2B] above.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| <u>Claim 3.</u><br><br>[G1-3A]<br>The compound of claim 2,<br><br><br>[G1-3B]<br>wherein the compound is selected from the group consisting of:<br><br><b>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate;</b><br><br>4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate); |                                         | See discussion for Ground 1, claim 2 above.<br><br><br>*****<br><b>Truelove 1 (EX1002)</b><br>As discussed in [G1-2A] above, Truelove 1, Table 3, EX1002, 9:26-38, copied below<br><br><table><tr><th colspan="4">TABLE 3</th></tr><tr><th rowspan="2">Compound</th><th colspan="3">Rate of hydrolysis in <math>t_{1/2}</math> seconds</th></tr><tr><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>L-3,4-diacetyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>20</td><td>45</td><td>180</td></tr><tr><td>L-3,4-dipropionyl-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol hydroperchlorate</td><td>50</td><td>90</td><td>240</td></tr><tr><td>L-3,4-dibutyryl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>100</td><td>160</td><td>360</td></tr><tr><td>L-3,4-dipivalyl-<math>\alpha</math>-[(methylamino)-methyl] benzyl alcohol hydroperchlorate</td><td>600</td><td>720</td><td>1,800</td></tr></table> |       | TABLE 3 |  |  |  | Compound | Rate of hydrolysis in $t_{1/2}$ seconds |  |  | Horse | Rabbit | Human | L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 20 | 45 | 180 | L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydroperchlorate | 50 | 90 | 240 | L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 100 | 160 | 360 | L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate | 600 | 720 | 1,800 |
| TABLE 3                                                                                                                                                                                                                                                                                                   |                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| Compound                                                                                                                                                                                                                                                                                                  | Rate of hydrolysis in $t_{1/2}$ seconds |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |       |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
|                                                                                                                                                                                                                                                                                                           | Horse                                   | Rabbit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Human |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-diacetyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                          | 20                                      | 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 180   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dipropionyl- $\alpha$ -[(methylamino)methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                        | 50                                      | 90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 240   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dibutyryl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                         | 100                                     | 160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 360   |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |
| L-3,4-dipivalyl- $\alpha$ -[(methylamino)-methyl] benzyl alcohol hydroperchlorate                                                                                                                                                                                                                         | 600                                     | 720                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1,800 |         |  |  |  |          |                                         |  |  |       |        |       |                                                                                  |    |    |     |                                                                                    |    |    |     |                                                                                   |     |     |     |                                                                                   |     |     |       |

| GROUND 1                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| CLAIMS<br>[Ground # - Claim ID]                                    | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; and | <p>discloses the corrected named diester compounds, namely “3,4-<del>diacetyl</del><b>acetox</b>y-<math>\alpha</math>-[(methylamino) methyl] benzyl alcohol” and “3,4-<del>dipropionyl</del><b>propionox</b>y-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol.”</p> <p>A POSA would have understood that “3,4-<b>diacetox</b>y-<math>\alpha</math>-[(methylamino) methyl] benzyl alcohol” has the alternative name of “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate”, and that “3,4-<b>dipropionox</b>y-<math>\alpha</math>-[(methylamino)methyl] benzyl alcohol” has the alternative name of “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate”. See, e.g., ChemDraw generated structures and displayed names below.</p> <div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%; text-align: center;">  <p>3,4-diacetox-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p> </div> <div style="width: 50%; text-align: center;">  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate</p> </div> <div style="width: 50%; text-align: center;">  <p>3,4-dipropionox-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p> </div> <div style="width: 50%; text-align: center;">  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate</p> </div> </div> <p>*****</p> |

| <b>GROUND 1</b><br><b>Truelove 1 (EX1002), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                                          |                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                              | <b>REFERENCES</b>                                                                                                  |
| [G1-3C]<br>a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film. | <b>Truelove 1 (EX1002), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b><br><br>See discussion for [G1-1A] above. |

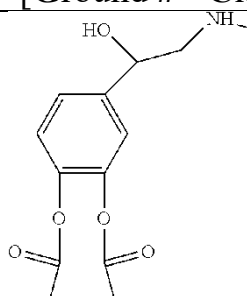
**GROUND 2**

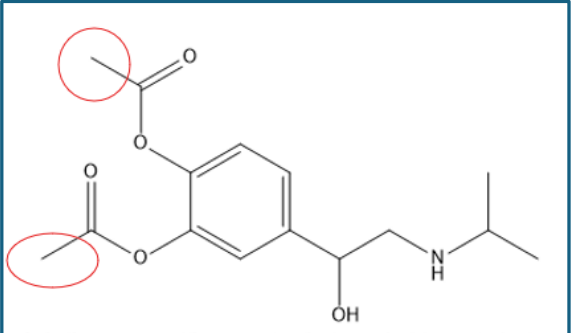
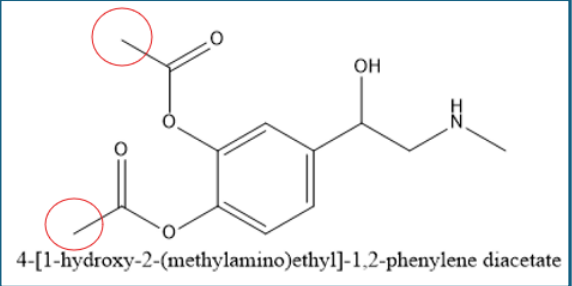
| GROUND 2                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------|--|--|----------|-----------------------------------------|--|--|-------|--------|-------|--------------------------------------------------------------------------------|----|----|-----|-------------------------------------------------------------------------------------|----|----|-----|---------------------------------------------------------------------------------|-----|-----|-----|---------------------------------------------------------------------------------|-----|-----|------|
| Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| CLAIMS<br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                                                                | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| <p>Claim 1.</p> <p>[G2-1A]<br/>A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration</p> <p>[G2-1B]<br/>of a Formula:</p> <div></div> <p>wherein R is selected from the group consisting of: —</p> | <p><b>Truelove 3 (EX1008)</b></p> <p>“The new compound and its non-toxic salts are thus administrable in the form of . . . buccal patches. . . .”. (EX1008, 7:35-39.)</p> <p><b>Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b><br/>See Almoazen Paper &amp; Ashraf discussion in [G1-1A] above.</p> <p>*****</p> <p><b>Truelove 3 (EX1008)</b></p> <p>Truelove 3, Table 3, EX1008, 10:58-70, copied below,</p> <div><table><tr><th colspan="4">TABLE 3</th></tr><tr><th rowspan="2">Compound</th><th colspan="3">Rate of Hydrolysis in <math>t_{1/2}</math> Seconds</th></tr><tr><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>3,4-diacetoxy-<math>\alpha</math>1[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>20</td><td>45</td><td>180</td></tr><tr><td>3,4-dipropionyloxy-<math>\alpha</math>1[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>50</td><td>90</td><td>240</td></tr><tr><td>3,4-dibutyroxy-<math>\alpha</math>1[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>100</td><td>160</td><td>360</td></tr><tr><td>3,4-dipivaloxy-<math>\alpha</math>1[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>600</td><td>720</td><td>1800</td></tr></table></div> | TABLE 3 |       |  |  | Compound | Rate of Hydrolysis in $t_{1/2}$ Seconds |  |  | Horse | Rabbit | Human | 3,4-diacetoxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 20 | 45 | 180 | 3,4-dipropionyloxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 50 | 90 | 240 | 3,4-dibutyroxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 100 | 160 | 360 | 3,4-dipivaloxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 600 | 720 | 1800 |
| TABLE 3                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| Compound                                                                                                                                                                                                                                                                                                                                                       | Rate of Hydrolysis in $t_{1/2}$ Seconds                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |       |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
|                                                                                                                                                                                                                                                                                                                                                                | Horse                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Rabbit  | Human |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| 3,4-diacetoxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                                                                                                                 | 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 45      | 180   |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| 3,4-dipropionyloxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                                                                                                            | 50                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 90      | 240   |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| 3,4-dibutyroxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                                                                                                                | 100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 160     | 360   |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |
| 3,4-dipivaloxy- $\alpha$ 1[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                                                                                                                | 600                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 720     | 1800  |  |  |          |                                         |  |  |       |        |       |                                                                                |    |    |     |                                                                                     |    |    |     |                                                                                 |     |     |     |                                                                                 |     |     |      |

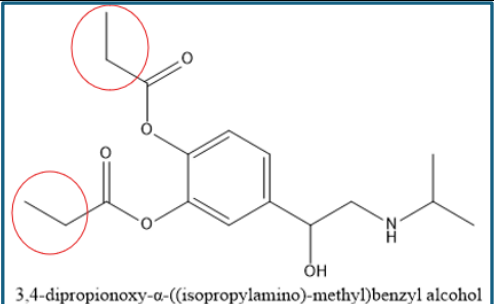
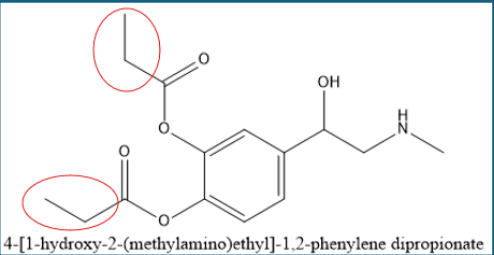
| GROUND 2                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| CLAIMS<br>[Ground # - Claim ID]                                                                                                                   | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p>***<br/> <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math>,<br/>           ***<br/>           or a pharmaceutically acceptable salt thereof,</p> | <p>discloses the diester isoproterenol compound “3,4-dibutyroxy-<math>\alpha</math>-[(isopropylamino)-methyl]benzyl alcohol hydrochloride” as well as its non-salt form “3,4-dibutyroxy-<math>\alpha</math>-[(isopropylamino)-methyl]benzyl alcohol”.</p> <p>A POSA would have understood that this compound in both salt and non-salt form corresponds to diester isoproterenol compounds where R substituents of the ester promoieties are <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math>. See ChemDraw® generated compound structure and displayed compound name below for the non-salt form for both isoproterenol (top) and epinephrine (bottom) with, in each case, the R Group <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math> circled.</p> <div style="text-align: center;">  <p>3,4-dibutyroxy-<math>\alpha</math>-((isopropylamino)-methyl)benzyl alcohol</p> </div> <div style="text-align: center;">  <p>3,4-dibutyroxy-<math>\alpha</math>-[(methylamino)methyl]benzyl alcohol</p> </div> |

| <b>GROUND 2</b>                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                 | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p>[G2-1C] wherein said compound has a <b>Log P value in the range of about 0.5-6.0</b> and</p> <p>[G2-1D] wherein the compound is</p> | <p>Because of isoproterenol's and epinephrine's structural similarity, a POSA would have understood that Truelove 3's disclosure of this diester isoproterenol compound and its associated half-life <math>t_{1/2}</math> teaches that the same ester promoiety with R substituent <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math> could be used to form the epinephrine prodrug compound "3,4-dibutyroxy-<math>\alpha</math>-[(methylamino)-methyl]benzyl alcohol", shown above, which has the same structure as recited in Claim 1 and which would have substantially the same, if not identical <math>t_{1/2}</math> of <b>360 seconds or 6 minutes</b>. The <math>t_{1/2}</math> of 360 seconds or 6 minutes falls within the claim limitation [G2-1E] below of a half-life <math>t_{1/2}</math> range from 1-6 minutes.</p> <p>*****</p> <p><b>Ashraf (EX1003)</b></p> <p>"Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of <b>log P</b> (octanol/water partition coefficient) <b>values of 1 to 5.</b>" (EX1003, p. 35, 2nd col., emphasis added).</p> <p>The inherent Log P of the claim 1 epinephrine compound with ester promoiety <b>R = <math>-\text{CH}_2\text{CH}_2\text{CH}_3</math></b> is +0.8. See, '437 Patent (EX1001), Table 1, 5:29..</p> <p>*****</p> |

| <b>GROUND 2</b>                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                           | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p>formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G2-1E.]<br/>has a <b>half-life <math>t_{1/2}</math> range from 1-6 minutes.</b></p> | <p><b>Truelove 3 (EX1008) &amp; Almoazen Paper (EX1022)</b></p> <p>See discussion in [G2-1A] above.</p> <p>*****</p> <p><b>Truelove 3 (EX1008)</b></p> <p>See discussion in [G2-1B] above for the disclosure in Truelove 3, Table 3 of compound where both R substituents of the ester promoieties of epinephrine are <b>-CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub></b> as disclosing to a POSA a epinephrine prodrug compound with a <b>half-life <math>t_{1/2}</math> of 6 minutes.</b></p> |
| <p><u>Claim 2.</u></p> <p>[G2-2A]<br/>A compound of a Formula</p>                                                                                                | <p><b>Truelove 3 (EX1008)</b></p> <p>Truelove 3, Table 3. Exhibit 1008, 10:58-70, copied below,</p>                                                                                                                                                                                                                                                                                                                                                                                            |

| GROUND 2                                                                                                                                                                                                                                                     |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|---------|--|--|--|----------|------------------------------------------------|--|--|-------|--------|-------|-----------------------------------------------------------------------|----|----|-----|----------------------------------------------------------------------------|----|----|-----|------------------------------------------------------------------------|-----|-----|-----|------------------------------------------------------------------------|-----|-----|------|
| Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)                                                                                                                                                                                             |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| CLAIMS                                                                                                                                                                                                                                                       |                                                | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| [Ground # - Claim ID]                                                                                                                                                                                                                                        |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| <div></div> <p>wherein R is selected from the group consisting of: <b>CH<sub>3</sub></b>, <b>CH<sub>2</sub>CH<sub>3</sub></b> and <b>CH(CH<sub>3</sub>)<sub>2</sub></b></p> |                                                | <div><table><tr><th colspan="4">TABLE 3</th></tr><tr><th rowspan="2">Compound</th><th colspan="3">Rate of Hydrolysis in t<sub>1/2</sub> Seconds</th></tr><tr><th>Horse</th><th>Rabbit</th><th>Human</th></tr><tr><td>3,4-diacetoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>20</td><td>45</td><td>180</td></tr><tr><td>3,4-dipropionyloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>50</td><td>90</td><td>240</td></tr><tr><td>3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>100</td><td>160</td><td>360</td></tr><tr><td>3,4-dipivaloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride</td><td>600</td><td>720</td><td>1800</td></tr></table></div> <p>discloses the salt form and thus the non-salt form of “3,4 diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol” and “3,4-dipropionyloxy-α-((isopropylamino)-methyl)benzyl alcohol”.</p> <p>A POSA would have understood that these compounds in both salt and non-salt form correspond to diester isoproterenol compounds where the R substituents of the ester promoieties are -<b>CH<sub>3</sub></b> and -<b>CH<sub>2</sub>CH<sub>3</sub></b>, respectively.</p> <p>Because of isoproterenol’s and epinephrine’s structural similarity, see structures below, a POSA would have understood that Truelove 3’s disclosure of these diester isoproterenol prodrug compounds and their associated half-lives t<sub>1/2</sub> teaches that the same ester promoieties with R substituents -<b>CH<sub>3</sub></b> and -<b>CH<sub>2</sub>CH<sub>3</sub></b>, could be used to form the epinephrine prodrug compounds of Claim 2, namely “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate” and “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate”.</p> |       | TABLE 3 |  |  |  | Compound | Rate of Hydrolysis in t <sub>1/2</sub> Seconds |  |  | Horse | Rabbit | Human | 3,4-diacetoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 20 | 45 | 180 | 3,4-dipropionyloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 50 | 90 | 240 | 3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 100 | 160 | 360 | 3,4-dipivaloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride | 600 | 720 | 1800 |
| TABLE 3                                                                                                                                                                                                                                                      |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| Compound                                                                                                                                                                                                                                                     | Rate of Hydrolysis in t <sub>1/2</sub> Seconds |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |       |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
|                                                                                                                                                                                                                                                              | Horse                                          | Rabbit                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Human |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| 3,4-diacetoxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                        | 20                                             | 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 180   |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| 3,4-dipropionyloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                   | 50                                             | 90                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 240   |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| 3,4-dibutyroxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                       | 100                                            | 160                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 360   |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |
| 3,4-dipivaloxy-α-[(isopropylamino)-methyl]benzyl alcohol hydrochloride                                                                                                                                                                                       | 600                                            | 720                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1800  |         |  |  |  |          |                                                |  |  |       |        |       |                                                                       |    |    |     |                                                                            |    |    |     |                                                                        |     |     |     |                                                                        |     |     |      |

| <p style="text-align: center;"><b>GROUND 2</b></p> <p style="text-align: center;"><b>Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)</b></p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p style="text-align: center;"><b>CLAIMS</b></p> <p style="text-align: center;">[Ground # - Claim ID]</p>                                                     | <p style="text-align: center;"><b>REFERENCES</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                                                                                                                                                               | <p>See ChemDraw® generated compound structures (showing their structural similarity) and displayed compound names for the non-salt form for isoproterenol (<b>top</b>) and epinephrine (<b>bottom</b>) prodrug compounds:</p> <p>with R = -CH<sub>3</sub> group circled below -</p> <div style="text-align: center;">  <p>3,4-diacetoxy-α-((isopropylamino)-methyl)benzyl alcohol</p> </div> <div style="text-align: center;">  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate</p> </div> <p>with R = -CH<sub>2</sub>CH<sub>3</sub> group circled below -</p> |

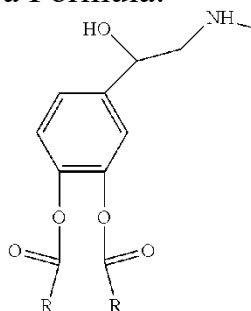
| GROUND 2                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| CLAIMS<br>[Ground # - Claim ID]                                                                       | REFERENCES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p>[G2-2B]<br/>wherein the compound is formulated in a unit dosage form as a sublingual or buccal</p> |  <p>3,4-dipropionyloxy-α-((isopropylamino)-methyl)benzyl alcohol</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                                                                       |  <p>4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate</p> <p>Thus, a POSA would have expected that the epinephrine prodrugs with the same ester promoieties as the isoproterenol prodrug compounds would have a similar if not identical half-lives of <math>t_{1/2} = 180</math> seconds (<b>3 minutes</b>) and <math>t_{1/2} = 240</math> seconds (<b>4 minutes</b>), <b>respectively</b>. These half-lives fall within the claim limitation [G2-2C] below of a half-life <math>t_{1/2}</math> range from 1-6 minutes.</p> <p>*****</p> <p><b>Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussed in [G2-1A] above for [G2-2B] disclosure.</p> |

| <b>GROUND 2</b>                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                     | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p>administration and wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G2-2C]<br/>has a <b>half-life <math>t_{1/2}</math> range from 1-6 minutes.</b></p> | <p>*****</p> <p><b>Truelove 3 (EX1008)</b></p> <p>See discussion in [G2-1B] above for the disclosure in Truelove 3, Table 3 of compounds where R substituents of the ester promoieties are <b>-CH<sub>3</sub></b> and <b>-CH<sub>2</sub>CH<sub>3</sub></b>, as disclosing to a POSA that epinephrine prodrugs with these ester promoieties have half-lives of <b><math>t_{1/2}</math> = 180 seconds (3 minutes) and <math>t_{1/2}</math> = 240 seconds (4 minutes), respectively.</b></p> |
| <p><u>Claim 3.</u></p> <p>[G2-3A]<br/>The compound of claim 2,</p> <p>[G2-3B]<br/>wherein the compound is selected from the group consisting of:</p>                                                       | <p>See discussion for Ground 2, claim 2 above.</p> <p>*****</p> <p>As discussed in [G2-2A] above, Truelove 3, Table 3. Exhibit 1008, 10:58-70, discloses diester promoieties that a POSA would have understood could be used to form the epinephrine prodrug</p>                                                                                                                                                                                                                          |

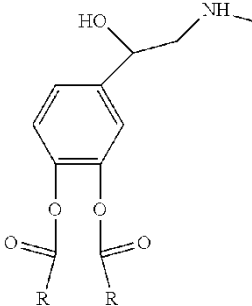
| <b>GROUND 2</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Truelove 3 (EX1008), Almoazen Paper (EX1022) and Ashraf (EX1003)</b>                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                 |
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>REFERENCES</b>                                                                                                                                                                                                                                                                               |
| <p><b>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene diacetate;</b></p> <p>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate) [diisobutyryl];</p> <p><b>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; and</b></p> <p>[G2-3C]<br/>a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.</p> | <p>compounds “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene diacetate” and “4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene dipropionate”.</p> <p>*****</p> <p><b>Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussion above got [G2-1A] above.</p> |

**GROUND 3**

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                  | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <u>Claim 1.</u><br><br><u>[G3-1A]</u><br>A compound formulated as a pharmaceutical composition in a unit dosage form configured for sublingual or buccal administration | <p><b>Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussions in [G1-1A] and [G2-1A] above.</p> <p><b>Fuchs (EX1004)</b></p> <p>Fuchs (EX1004) teaches unit dosage films (EX1004, 2:65-5:6) and provides many examples of various suitable film compositions having various characteristics (EX1004, 5:7-14:24). See also, EX1001, 2:39-46.</p> <p><b>Schobel (EX1021)</b></p> <p>Schobel (EX1021) teaches the use and methods of making oral rapidly dissolving films for delivery of epinephrine compositions including epinephrine prodrugs to the oral mucosa. <i>See, e.g.</i>, EX1021, 1:17-46 (epinephrine in films), 13:37-67 (rapidly dissolving films), 13:15-67 &amp; 16:57-27:2 (oral dissolving films), 14:13-18 (drug in form of prodrug), 15:62-65 &amp; 45:19-20 (ester prodrugs of epinephrine).</p> |

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                                                                                                        | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p>[G3-1B]<br/>of a Formula:</p>  <p>wherein R is selected from the group consisting of: —<br/>***<br/><b>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,</b><br/>***<br/>or a pharmaceutically acceptable salt thereof,</p> <p>[G3-1C]<br/>wherein said compound has a <b>Log P value in the range of about 0.5-6.0</b> and</p> | <p>*****</p> <p><b>Truelove 1 (EX1002) &amp; Truelove 3 (EX1008)</b></p> <p>A POSA would have understood that Truelove 1, Table 3 and Truelove 3, Table 3 each disclose the diester promoiety where the R substituent is - <b>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub></b>, and that this promoiety could be used to form the recited epinephrine prodrug compound.</p> <p>See discussions in [G1-1A] and [G2-1A] above.</p> <p>*****</p> <p><b>Ashraf (EX1003)</b></p> <p>“Satisfactory oral [mucosal] absorption of drugs has been observed over a wide range of <b>log P</b> (octanol/water partition coefficient) <b>values of 1 to 5.</b>” (EX1003, p. 35, 2nd col., emphasis added).</p> |

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                     | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p>[G3-1D]<br/>wherein the compound is formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G3-1E]<br/>has a <b>half-life</b> <math>t_{1/2}</math> <b>range from 1-6 minutes.</b></p> | <p>The inherent Log P of the claim 1 epinephrine compound with the ester promoiety <b>R = -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub></b> is +0.8. See, '437 Patent (EX1001), Table 1, 5:29.</p> <p style="text-align: center;"><b>Florence (EX1015)</b></p> <p>Florence (EX1015) at Table 9.1, p. 350, teaches that the ideal log P values for buccal absorption typically range in bases from 3.52 (dissociated) to 5.52 (undissociated) and in acids 4.19 (undissociated), varying based on the chemical characteristics of the absorbing molecule.</p> <p style="text-align: center;">*****</p> <p style="text-align: center;"><b>Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussions in [G1-1A] and [G2-1A] above.</p> <p style="text-align: center;"><b>Fuchs (EX1004) &amp; Schobel (EX1021)</b></p> <p>See discussion in [G3-1A] above.</p> <p style="text-align: center;">*****</p> <p style="text-align: center;"><b>Truelove 1 (EX1002) &amp; Truelove 3 (EX1008)</b></p> <p>See discussions in [G1-1E] and [G2-1E] above.</p> |

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><u>Claim 2.</u></p> <p>[G3-2A]<br/>A compound of a Formula</p>  <p>wherein R is selected from the group consisting of: <b>CH<sub>3</sub></b>, <b>CH<sub>2</sub>CH<sub>3</sub></b> and <b>CH(CH<sub>3</sub>)<sub>2</sub></b></p> <p>[G3-2B]<br/>wherein the compound is formulated in a unit dosage form as a sublingual or buccal administration and wherein the compound is</p> | <p><b>Truelove 1 (EX1002) &amp; Truelove 3 (EX1008)</b></p> <p>A POSA would have understood that Truelove 1, Table 3 and Truelove 3, Table 3 each disclose the diester promoieties where the R substituents are - <b>CH<sub>3</sub></b> and -<b>CH<sub>2</sub>CH<sub>3</sub></b>, and that these promoieties could be used to form the recited epinephrine prodrug compounds.</p> <p>See discussions in [G1-2A] and [G2-2A] above.</p> <p>*****</p> <p><b>Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussions in [G1-1A] and [G2-1A] above.</p> <p><b>Fuchs (EX1004) &amp; Schobel (EX1021)</b></p> |

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                                                          |                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                 | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                |
| <p>formulated in a unit dosage form as a rapidly dissolving film and</p> <p>[G3-2C]<br/>has a <b>half-life <math>t_{1/2}</math> range from 1-6 minutes.</b></p>                                        | <p>See discussion in [G3-1A] above.</p> <p>*****</p> <p><b>Truelove 1 (EX1002) &amp; Truelove 3 (EX1008)</b></p> <p>See discussions in [G1-1C] and [G2-1C] above.</p>                                                                                                                                                                            |
| <p><u>Claim 3.</u></p> <p>[G3-3A]<br/>The compound of claim 2,</p> <p>[G3-3B]<br/>wherein the compound is selected from the group consisting of:</p> <p><b>4-(1-hydroxy-2-(methylamino)ethyl)-</b></p> | <p>See discussion for Ground 3, claim 2 above.</p> <p>*****</p> <p><b>Truelove 1 (EX1002) &amp; Truelove 3 (EX1008)</b></p> <p>See discussion in [G1-3B] and [G2-3B] above that EX1002, Table 3 and EX1008, Table 3 disclose the ester promoieties that would form the following recited compounds: “4-(1-hydroxy-2-(methylamino)ethyl)-1,2-</p> |

| <b>GROUND 3 – Truelove 1, Truelove 3, Almoazen Paper, Ashraf, Fuchs, Florence and Schobel</b>                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>CLAIMS</b><br>[Ground # - Claim ID]                                                                                                                                                                                                                                                                                                                                                               | <b>REFERENCES</b>                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>1,2-phenylene di-acetate;</b></p> <p>4-(1-hydroxy-2(methylamino)ethyl)-1,2-phenylene bis(2-methylpropanoate);</p> <p><b>4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate; and</b></p> <p>[G3-3C]<br/>a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient, wherein the compound is formulated in a unit dosage form as a rapidly dissolving film.</p> | <p>phenylene di-acetate” and “4-(1-hydroxy-2-(methylamino)ethyl)-1,2-phenylene dipropionate”.</p> <p>*****</p> <p><b>Truelove 1 (EX1002) , Truelove 3 (EX1008), Almoazen Paper (EX1022) &amp; Ashraf (EX1003)</b></p> <p>See discussions in [G1-1A] and [G2-1A] above.</p> <p><b>Fuchs (EX1004) &amp; Schobel (EX1021)</b></p> <p>See discussion in [G3-1A] above.</p> |

**XV. CONCLUSION**

Petitioner respectfully requests institution of *Inter Partes* Review of claims 1-3 of U.S. Patent No. 11,021,437, followed by a grant of this Petition and cancellation of claims 1-3 on the Grounds detailed above.

Dated: May 16, 2025

Respectfully,

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**XVI. CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,988 words out of 14,000, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a) (that is, the word count does not include the table of contents, table of authorities, the exhibit list, mandatory notices under 37 C.F.R. § 42.8, the certificate of service, or the certificate of compliance).

Dated: May 16, 2025

Respectfully,

/Michael I. Chakansky/

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**XVII. CERTIFICATE OF SERVICE**

I hereby certify that on this 16<sup>th</sup> day of May, 2025, the foregoing PETITION FOR INTER PARTES REVIEW UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.1 ET SEQ., including all Exhibits and the Power of Attorney, were served pursuant to 37 C.F.R. § 42.6 and 37 C.F.R. § 42.105, via FedEx® overnight delivery or Priority Mail Express, on the following:

Patent Owner Correspondence Address of Record (37 C.F.R. § 42.105(a)):

Susan B. Frentress  
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PO BOX 770029  
Memphis, Tennessee 38117

-and-

Patent Owner (37 C.F.R. § 42.6(e)(2) and 37 C.F.R. § 42.105(a)):

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