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Patent Owner's Demonstratives

Dr. Reddy's Lab'ys S.A. v. Eye Therapies, LLC, IPR2024-00467, IPR2024-00563

Summary of Responses to Petitioners' Arguments

’245 and ’600 Patent Claims Meaningfully Differ from the ’742 Patent Claims as Construed by the Prior Board

Requires separate and independent adjudication by this Board

’742 Claims

Permitting co-administration of 0.03% brimonidine with other active ingredients, even if they can reduce redness, and no requirement of efficacy

’600 Patent

Low dose of 0.025% brimonidine as the ***sole active agent*** to actually reduce eye redness

- Open to multiple drops that do not exceed an amount of drug a single drop of 0.05% brimonidine would ocularly deliver

’245 Patent

Single step of administering a ***single drop*** of 0.025% brimonidine as the ***sole active agent*** plus benzalkonium chloride (preservative) to actually reduce redness

- Consistently tethered to the specification and prosecution history
- ’742 IPR FWD submitted in an IDS

No Estoppel

- No final decision from the CAFC
- Petitioners’ estoppel cases are inapposite

245 IPR: Paper 25 at 3-6, 11-13, and 36, Paper 72 at 2-10;
600 IPR: Paper 21 at 3-7, Paper 68 at 2.

Additional Efficacy Limitations Further Restricting the ’245 Patent Claims

- “wherein the ocular drop induces a low incidence of rebound hyperemia in the eye of the human subject administered the ocular drop.”
- “wherein the eye redness of said human is not associated with an ocular disease or the result of a surgical procedure on the eye.”
- “wherein the method retains normal intraocular pressure in the eye of the human subject administered the ocular drop.”
- “wherein the eye redness of said human is not associated with an ocular disease or the result of a surgical procedure on the eye, wherein the ocular drop reduces redness in the eye to which the ocular drop was administered to improve the aesthetic appearance of said eye and wherein the method retains normal intraocular pressure in the eye of the human subject administered the ocular drop.”

Patent Owner's Experts



Robert J. Noecker, M.D., MBA

- Board-certified ophthalmologist specializing in glaucoma with over 30 years of experience
- Has participated in multiple clinical trials for ophthalmic medications and is **the only expert in this proceeding who has served as a principal investigator in the Alphagan® (brimonidine) clinical trial**
- Has been selected to the Best Doctors in America every year since 2004



Daniel W. Gil, Ph.D.

- Worked at Allergan in various positions for over 30 years
- Led **Allergan's** alpha-adrenergic discovery team and oversaw teams of researchers in drug discovery, including in **drug repurposing**, pain, and drugs acting on alpha-adrenergic receptors
- **Lead inventor on the "Gil patent," U.S. Patent No. 6,294,553 entitled *Methods for Treating Ocular Pain***



Kurt R. Karst, Esq.

- Has over 25 years of legal experience and **specializes in food and drug law, including prescription and over-the-counter (OTC) drug and biological product approval**, licensure, and marketing
- Has handled thousands of FDA matters for hundreds of clients, including counseling on the FDCA, Hatch-Waxman Amendments, and other FDA-related laws and regulations

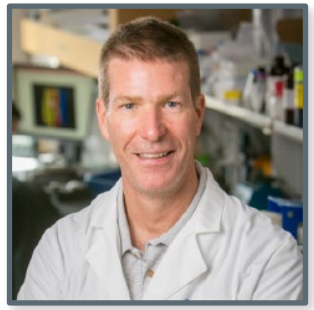
EX2223 (Noecker Decl.) at ¶¶ 6-17; EX2227 (Gil Decl.) at ¶¶ 3-6;
EX2228 (Karst Decl.) at ¶¶ 4-10

Patent Owner's Experts cont.



Eric D. Donnenfeld, M.D.

- Board-certified ophthalmologist specializing in anterior segment, including corneal disease, corneal transplantations, cataract, and LASIK
- **Has performed over 100,000 LASIK procedures throughout his career and was one of the first to ever perform the procedure over 35 years ago**
- Has participated in over 40 FDA clinical studies



W. Daniel Stamer, Ph.D.

- **Recognized expert in ocular pharmacology and physiology with over 30 years of experience**
- Has authored over 250 publications and has held multiple editorial appointments
- In 2023, Dr. Stamer was inducted into the Glaucoma Research Society, which is limited to the top 100 glaucoma researchers in the world



John C. Jarosz

- Has testified regarding economic issues on over 110 occasions over the last 35 years
- **Has testified in more than 45 cases on the issue of commercial success**
- More than 25 peer-reviewed publications on economic and legal topics
- M.A. Economics, Washington University in St. Louis; J.D., University of Wisconsin

EX2224 (Donnenfeld Decl.) at ¶¶ 4-13; EX2225 (Stamer Decl.) at ¶¶ 1-7; EX2229 (Jarosz Decl.) at ¶¶ 5-9

Dose ≠ Concentration

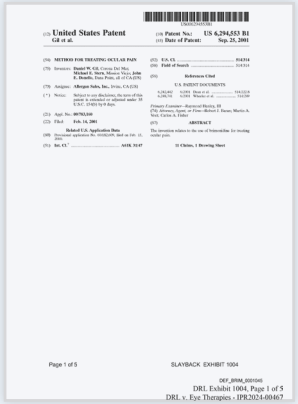
Dose Matters for Efficacy

- The ’245 and ’600 patent claimed methods of reducing eye redness use low-dose brimonidine
- Dose and concentration are different
  - Dose = total amount of drug ocularly delivered
    - depends on concentration and dosage regimen, e.g., number of drops instilled
  - Concentration = amount of drug in a given volume
- Dose is what matters for the therapeutic effect
  - DRL acknowledges that dose matters in asserting POSAs would be motivated to “pursue low-dose brimonidine” to reduce eye redness. *See, e.g.*, Paper 2 at 2.

245 IPR: Paper 25 at 13, Paper 72 at 2-5.

Impact of Different Scope of the ’245 and ’600 Patents in Distinguishing Prior Art

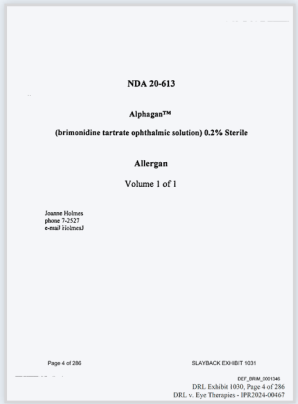
Steady and consistent prior art messaging: ***Dose HIGH*!**



- **Gil (EX1004)**
  - Example 1: dose-loading protocol administering ***6-7*** drops of 0.03% → a dose of ~***0.2***%
    - ***8x*** higher than ’245 patent claim 1
  - Examples 4 and 5: 1 cc (***20-30*** drops) x (0.01-0.5%) → a dose of ~0.2% to 0.3% (at the lowest concentration)



- **Norden (EX1006):**
  two drops x ***0.2***% → a dose of ~***0.4***% brimonidine
  - ***16x*** higher than ’245 patent claim 1

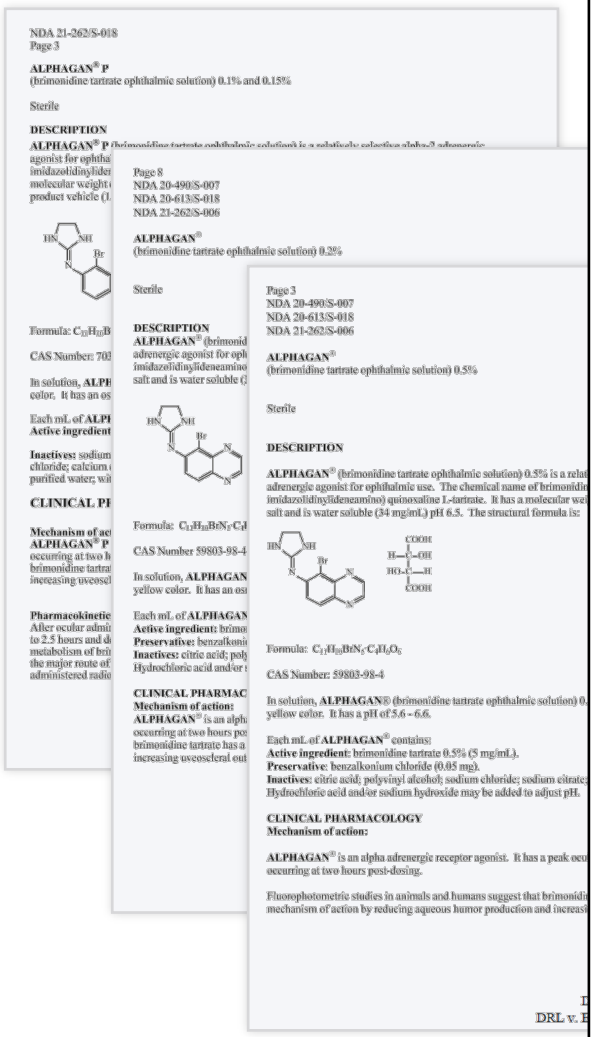


- **Alphagan Clinical Studies**
  - Highly relevant and reliable human trials consistently taught GO HIGH!
  - Dosing ***below 0.2% brimonidine did not*** induce sufficient vasoconstriction to reduce eye redness

EX1030, EX1067, EX1068, EX1029

245 IPR: Paper 25 at 24-35 and 38-48, Paper 72 at 13-14 and 19-25;
600 IPR: Paper 21 at 22-26, 30-43, Paper 68 at 5-6 and 11-17;
EX1030; EX1067; EX1068; EX1029

What Pre-2008 POSAs Would Have Known From Real, Not Prophetic, Clinical Studies Evaluating Brimonidine's Whitening Effect


NDA 21-262/S-018
Page 3

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

Page 8
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

Page 3
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.
yellow color. It has a pH of 5.6 - 6.6.

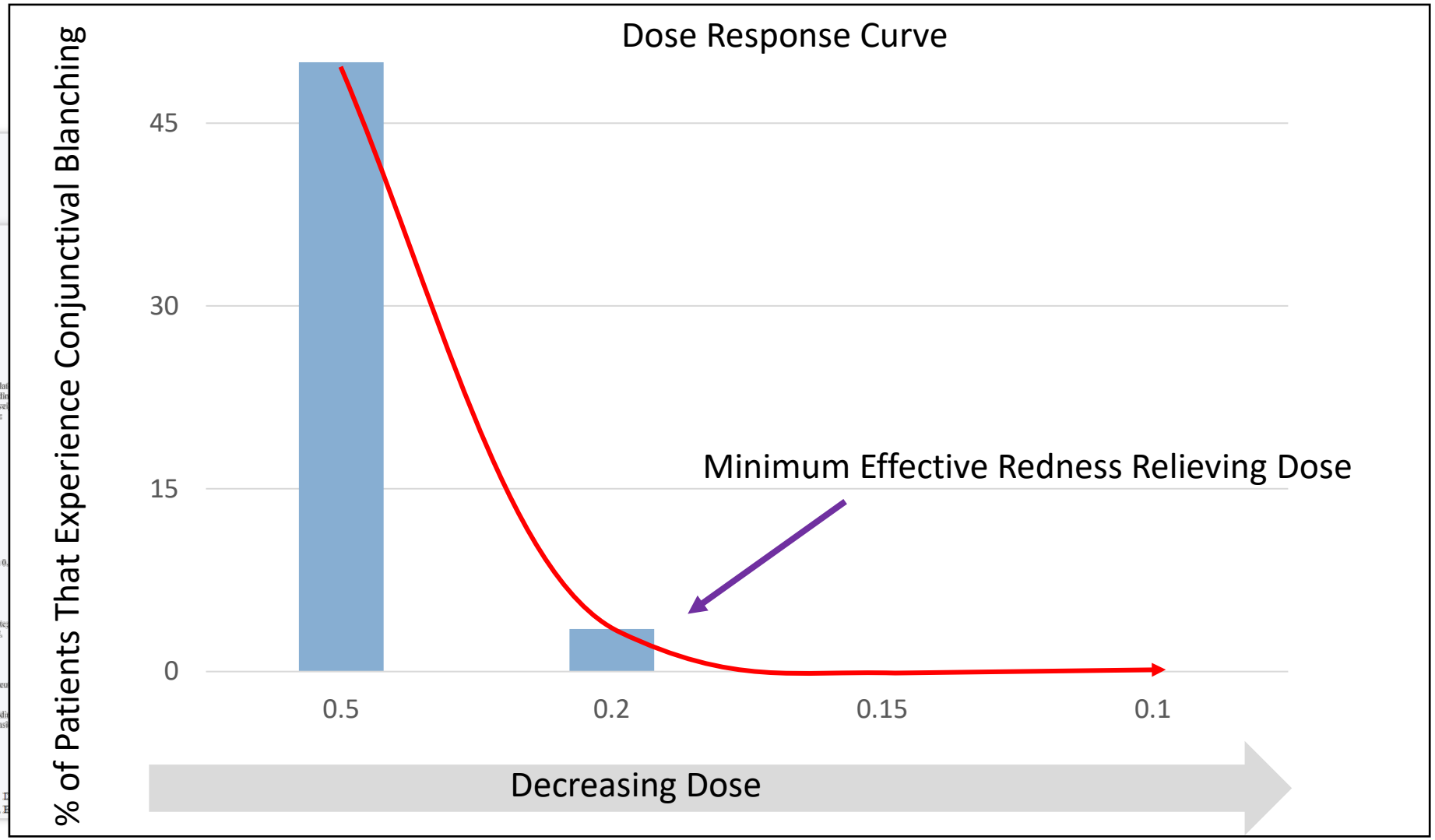
Each mL of ALPHAGAN® contains:
Active ingredient: brimonidine tartrate 0.5% (5 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate;
Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY
Mechanism of action:

ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocu
occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidi
mechanism of action by reducing aqueous humor production and increas

DRL v. E



EX1067 (ALPHAGAN® Labels); EX1068 (ALPHAGAN® P Label)

245 IPR: Paper 25 at 45 and 48, Paper 72 at 14 and 20-21;
600 IPR: Paper 21 at 39 and 42, Paper 68 at 6 and 12-13.

Impact of Different Scope of the ’245 and ’600 Patents in Distinguishing Prior Art

Dean (EX1007)



US006242442B1

(12) **United States Patent**
Dean et al.

(10) **Patent No.: US 6,242,442 B1**
(45) **Date of Patent: Jun. 5, 2001**

(54) **BRINZOLAMIDE AND BRIMONIDINE FOR TREATING OCULAR CONDITIONS**

(75) Inventors: **Thomas R. Dean**, Weatherford; **Louis Desantis, Jr.**, Fort Worth; **Billie M. York**, Conroe, all of TX (US)

(73) Assignee: **Alcon Laboratories, Inc.**, Fort Worth, TX (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/601,634**

(22) PCT Filed: **Dec. 7, 1999**

(86) PCT No.: **PCT/US99/28987**

§ 371 Date: **Aug. 4, 2000**

§ 102(e) Date: **Aug. 4, 2000**

(51) **Int. Cl.**[7] **A67K 31/535**

(52) **U.S. Cl.** **514/222.8**; 514/912; 514/913; 514/226.5; 514/363

(58) **Field of Search** 514/363, 222.8, 514/226.5, 912, 913

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,890,319	6/1975	Danielewicz et al.	260/256.4
5,378,703	1/1995	Dean et al.	514/222.8
5,756,503	5/1998	Bothe et al.	514/249
5,948,801	9/1999	Doshi et al.	514/363

FOREIGN PATENT DOCUMENTS

WO96/13267 * 5/1996 (WO) .
96/37203 11/1996 (WO) .
97/01339 1/1997 (WO) .

OTHER PUBLICATIONS

Gruswald, et al., Acta Ophthalmologica Scandinavica, vol. 75:236–238, 1997.
Pillinat, et al., ARVO abstract, Investigative Ophthalmology & Visual Science, vol. 38(4):S276, Abstract 1284, Mar. 15, 1997.
Shipman, et al., ARVO abstract, Investigative Ophthalmology & Visual Science, vol. 38(4):S783, Abstract 3633, Mar. 15, 1997.
Kollet, et al., ARVO abstract, Investigative Ophthalmology & Visual Science, vol. 38(4):S776, Abstract 3592, Mar. 15, 1997.
Harris, et al., Acta Ophthalmologica Scandinavica, vol. 74:569–572, 1996.
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Sponsel, et al., ARVO abstracts, Investigative Ophthalmology & Visual Science, vol. 37(3):S269, Abstract 1238, Feb. 15, 1996.
Sponsel, et al. ARVO abstracts, Investigative Ophthalmology & Visual Science, vol. 38(4):S439, Abstract 2078, Mar. 15, 1997.

* cited by examiner

Primary Examiner—Zohreh Fay
(74) *Attorney, Agent, or Firm*—Sally S. Yeager

(57) **ABSTRACT**

Methods and compositions for treating ocular conditions which find their etiology in compromised ocular blood flow with brinzolamide and brimonidine are disclosed.

4 Claims, No Drawings

Page 1 of 6

SLAYBACK EXHIBIT 1007

DEF_BRIM_0001061
DRL Exhibit 1007, Page 1 of 6
DRL v. Eye Therapies - IPR2024-00467

- Nothing about redness reduction
- Dataless hypothesis that brimonidine, at any concentration, vasoconstricts anterior segment of eye
- Pre-August 2008 POSAs understood from the Alphagan clinical trials that dosing brimonidine below ~0.2% would not have induced sufficient vasoconstriction to reduce redness

245 IPR: Paper 25 at 33-35, Paper 72 at 22;
600 IPR: Paper 21 at 30-32, Paper 68 at 14.

No Presumption of Obviousness of 0.025% Brimonidine

- **Together, Gil and Dean cover every known concentration of brimonidine**
  - Covering everything effectively tells POSAs nothing
    - *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (where "'the disclosed range[s are] so broad as to encompass a very large number of possible distinct compositions,' … such that they do not teach any specific amounts or combinations", the overlapping ranges presumption does not exist)

- **Teaching away and objective indicia evidence**
  - ***Dissolves*** overlapping ranges presumption and requires considering all evidence anew
    - *In re Kumar*, 418 F.3d 1361, 1366, 1368 (Fed. Cir. 2005) ("When rebuttal evidence is provided, the *prima facie* case ***dissolves***, and the decision is made on the entirety of the evidence.") (emphasis added).

245 IPR: Paper 25 at 40 and 54-61, Paper 72 at 24-27; Paper 6 at 3
600 IPR: Paper 21 at 34 and 50-57, Paper 68 at 16-19; Paper 6 at 4.

No Presumption of Obviousness of 0.025% Brimonidine

- **Teaching away**
  - Prior art blazemarks taught go high ≥ 0.2% brimonidine to reduce eye redness and against dosing below the minimum effective redness-relieving dose of 0.2% brimonidine

- **Objective indicia**
  - Unexpected results – low dose brimonidine not expected to work
    - Unexpectedly and beneficially, one drop 0.025% brimonidine reduced redness ***6x greater*** than standard of care, Visine, without rebound or tachyphylaxis
    - The unexpected results are different in kind
      - *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306-07 (Fed. Cir. 2015) (claimed invention demonstrating a difference between an effective and safe drug versus one with significant side effects that led to patient noncompliance "is an unexpected difference in kind that supports non-obviousness.")
  - Superior efficacy and safety profile of claimed method (embodied in use of Lumify) led to industry praise and then to commercial success

245 IPR: Paper 25 at 18, 28-29 and 54-61, Paper 72 at 21-27;
600 IPR: Paper 21 at 19, 30-31, and 50-57, Paper 68 at 14-19.

Inherency of 0.025% Brimonidine to Reduce Redness Undermined



"The unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness."

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1307 (Fed. Cir. 2015)

245 IPR: Paper 25 at 38-40, Paper 72 at 24-25;
600 IPR: Paper 25 at 34, Paper 68 at 16-17.

The ’245 and ’600 Patent Claims Are Different From the ’742 Patent Claims

’742 Patent Claims as Construed by the Board – “Consisting Essentially of”

“Thus, having considered the arguments and evidence presented at trial, we determine that the transitional phrase ‘consisting essentially of' does not preclude the use of additional active agents that may also cause vasoconstriction and reduction of hyperemia along with low-dose brimonidine.”

EX1003 (’742 FWD) at 15-16

- Permits other active ingredients, even if they can reduce eye redness
- Open to multiple drops, though low dose
- Concentration in drop encompasses 0.03% (claim 3)
- Preamble is limiting only to intent to reduce eye redness, no requirement of actual redness reduction

245 IPR: Paper 25 at 5-6, 36; 600 IPR: Paper 21 at 5-7.

The ’245 Patent: Claim 1 – “Consisting of”

1. A method for reducing eye redness in a human subject having ocular hyperemia, consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient, and one or more non-therapeutic components including benzalkonium chloride, wherein the ocular drop has a pH between 5.5 to 6.5, wherein the ocular hyperemia is reduced.

- Brimonidine as the sole active ingredient used in the method of reducing eye redness
- A single step, single drop of 0.025% brimonidine
- Bullet-point amount (dose) of 0.025% brimonidine
- Preamble read in light of claim body requires actual reduction in eye redness

245 IPR: Paper 25 at 3-6, 11-13, Paper 72 at 2-10.

The ’600 Patent Claims 1, 12, and 28 – “Comprising”

> 1. A method for reducing eye redness in a human subject having ocular hyperemia, comprising topically administering to an eye of said human in need of said reduction of eye redness an ocular drop comprising about 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5.

- Brimonidine as the sole active ingredient
- Bullet-point concentration of 0.025% (claim 28)
- Low dose of brimonidine – permits multiple drops not exceeding the total amount of brimonidine one drop of 0.05% brimonidine (top end of “low dose”) ocularly delivers

600 IPR: Paper 21 at 3-7, 11-14, Paper 68 at 2.

The POSA:
Views Prior Art With an Eye Toward Obtaining FDA Approval of an Improved Redness Reliever

Definition of the POSA Provides the Framework for Assessing Obviousness



"[D]efinition of the ***relevant artisan provid[es] the perspective that governs the obviousness analysis*** and of the problem addressed by the [claimed invention]."

Axonics, Inc. v. Medtronic, Inc., 73 F.4th 950, 958 (Fed. Cir. 2023)

- Petitioners' definition of POSA:
  - "a composite person (or team) that included a medical doctor and pharmaceutical formulator"
  - with ***collectively 6-9 years*** "***of experience*** developing eye drop formulations for ***clinical trial and regulatory approval***"

245 IPR: Paper 2 at 16-17; 600 IPR: Paper 2 at 16

245 IPR: Paper 25 at 10, 15-16; 600 IPR: Paper 21 at 11, 16-17.

POSAs Looking to Develop Improved Redness Relievers Motivated to Choose Pathway Likely to Result in FDA Approval

- *For pharmaceutical inventions, the law sanctions considering as relevant what a POSA would have done to develop an FDA approved product*



"Part of the obviousness inquiry involves examining what a skilled artisan would be motivated to do given 'the effects of demands known to the design community or present in the marketplace.' The district court thus did not err in considering the obviousness inquiry from the perspective of a skilled artisan 'confronted with the same problems as the inventor,' which in this case is developing a commercially viable long-acting testosterone therapy."

Endo Pharms. Sols., Inc. v. Custopharm Inc., 894 F.3d 1374, 1385-86 (Fed. Cir. 2018)

- *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291-92 (Fed. Cir. 2013) ("FDA approval may be relevant to the obviousness inquiry" such as "in determining whether one of ordinary skill would be motivated to develop a drug product."); *accord Bayer Pharma AG v. Watson Lab'ys, Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017).

245 IPR: Paper 25 at 15-17; 600 IPR: Paper 21 at 16-18.

Petitioners' Expert, Dr. Galanis, Admitted as Much



John Galanis, MD, FACS
(Petitioners' Expert)

Q. So you would agree that that [the skilled] person as you've defined them is inherently a practical person that is looking at this prior art, as you said, with respect to trying to develop a redness reliever, correct?

A. That would be correct.

Q. And that would be ultimately for developing a commercially approved redness reliever, correct?

A. That would be -- I assume that would be their intention.

Q. Okay. And, therefore, [POSAs] would look at the prior art to see what would reasonably work for purposes of trying to develop a commercially approved redness reliever; is that fair?

A. I think that would be a fair assessment, yes.

EX2017 (Galanis PI Dep. Tr.) at 83:10-84:2

245 IPR: Paper 25 at 15-16, 17; 600 IPR: Paper 21 at 16-17, 18.

’245 Patent Claim Construction

’245 Patent Claim 1: Single Step, Single Drop of 0.025% Brimonidine

1. A method for reducing eye redness in a human subject having ocular hyperemia, consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient, and one or more non-therapeutic components including benzalkonium chloride, wherein the ocular drop has a pH between 5.5 to 6.5, wherein the ocular hyperemia is reduced.

245 IPR: EX1001 (’245 Patent), 22:36-44

- Transitional phrase “consisting of” limits the claimed method to:
  - “ocularly administering ***a single drop of 0.025% brimonidine*** as the only active ingredient in ***a single step***, where the single step is the only step taken to reduce eye redness”

245 IPR: Paper 25 at 11-13, Paper 72 at 2-10.

Established Legal Meaning of "Consisting of"

"'Consisting of' is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim."

Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1331 (Fed. Cir. 2004)

245 IPR: Paper 25 at 11-13; *see also* Paper 72 at 3-4.

Prosecution History – Claim 1 (application claim 29) As-filed

29. (New) A method for reducing eye redness in a human subject having ocular hyperemia, comprising topically administering to an eye of said human in need of said reduction of eye redness an ocular drop comprising about 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5, wherein the ocular drop is preservative free.

245 IPR: EX1010 ('245 Patent File History) at 4

- Transitional phrase "comprising" opened the claim to:
  - one or more steps of administering
  - one or more drops
  - of 0.025% brimonidine as the sole active ingredient

245 IPR: Paper 25 at 12-13.

Prosecution History – Claim 1 As Allowed

1. A method for reducing eye redness in a human subject having ocular hyperemia, consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient, and one or more non-therapeutic components including benzalkonium chloride, wherein the ocular drop has a pH between 5.5 to 6.5, wherein the ocular hyperemia is reduced.

245 IPR: EX1001 ('245 Patent), 22:36-44

- Transitional "consisting of" closed the method to:
  - a single step (all parties agree), and
  - a single ocular drop, as ***the subject*** of what is ***administered*** in the single step

245 IPR: Paper 25 at 11-13, Paper 72 at 8-9.

Replacing Transition "Comprising" with "Consisting of" Was Made to Induce the Patent Grant

[00143]. We note that the transitional phrase "consisting of" between the preamble and the body of claim 29 means that brimonidine is the sole active ingredient administered in the method for reducing redness of claim 29, and excludes other active ingredients (such as steroids, anesthetics, carbonic anhydrase inhibitors, or NSAIDS, for example) from the method.

245 IPR: EX1010 ('245 Patent File History) at 288

- The excluded active ingredients come from:
  - Norden and Gil: steroids, NSAIDs, and anesthetics
  - Dean: carbonic anhydrase inhibitors

245 IPR: Paper 25 at 12-13.

Legal Consequence of Replacing Transition "Comprising" with "Consisting of"

Patentee surrendered claim scope beyond a single step a single drop!

"In particular, this court has interpreted the word 'a' in its singular sense when, as in this case, it has been used in conjunction with the closed transitional phrase 'consisting of.'

...

Thus, the claim language 'consisting of ... *a* sodium phosphate,' on its own, suggests the use of a single sodium phosphate."

Norian Corp. v. Stryker Corp., 432 F.3d 1356, 1359 (Fed. Cir. 2005)

- *Abbott Lab'ys v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1281 (Fed. Cir. 2003) ("[A]lthough 'a' without more generally could mean one or more in an open-ended patent claim, 'a' with 'consisting of' in this case indicates only one member of a Markush group.")

245 IPR: Paper 25 at 12-13, Paper 72 at 2-3.

DNJ Judge Robert Kirsch Agreed with the Single Step, Single Drop Construction

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE LUMIFY

Civil Action No. 21-16766 (RK) (RLS)
(CONSOLIDATED)

OPINION FILED UNDER TEMPORARY SEAL

KIRSCH, District Judge

This Hatch-Waxman action arises from the filing of an Abbreviated New Drug Application ("ANDA") by Defendants Dr. Reddy's Laboratories S.A., Dr. Reddy's Laboratories, Inc (collectively, "Dr. Reddy's" or "DRL"), Slayback Pharma LLC, Slayback Pharma India LLP (collectively "Slayback," and together with Dr. Reddy's, "Defendants"),[1] who seek to bring to market a generic version of a popular eye redness relieving eyedrop. Plaintiffs Bausch & Lomb, Inc., Bausch & Lomb Ireland Limited (collectively, "Bausch"), and Eye Therapies, LLC (together with Bausch, "Plaintiffs") contend Defendants' generic will infringe on United States Patent No. 11,833,245 (the "'245 patent").[2] This patent is directed to a method of treating eye redness with brimonidine tartrate, 0.025%, the active ingredient in Bausch's Lumify eyedrop. Lumify is the first eyedrop, and currently only on the market, to use low dose brimonidine tartrate to treat eye redness and is available over-the-counter.

After receiving notice of Defendants' ANDA, Plaintiffs immediately filed suit for patent infringement, thereby triggering an automatic thirty-month stay that barred Defendants from

[1] Slayback is Dr. Reddy's "predecessor-in-interest." (*See* ECF No. 178 at 6.)
[2] Bausch licenses the '245 patent from Eye Therapies, LLC. (*See* ECF No. 236 ¶ 142.)

Eye Therapies Exhibit 2030, 2 of 69
Dr. Reddy's v. Eye Therapies - IPR2024-00467

i. First "Consisting Of"

The first phrase of the claim at issue recites a method "consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop . . . ." ('245 patent at 22:37–39.) The Court agrees with Defendants that the use of "consisting of" here describes one single step—topically administering an eye drop to a human to reduce eye redness. The closed term excludes any other steps aside from those that are explicitly set forth in the claim. *See Multilayer Stretch Cling Film Holdings*, 831 F.3d at 1358. Plaintiffs do not appear to dispute this construction. Plaintiffs contend that "[t]he first 'consisting of' in claim

testimony that this was not a "true controlled trial." (*Id.* at 59:5–15.) Finally, as Dr. Donnenfeld explained, Norden used .2% brimonidine that had a "concentration [that] was eight times higher" and "patients received two drops fifteen minutes prior to surgery and five minutes prior to surgery," exposing the patient to significantly greater levels than a single drop of .025% brimonidine. (Tr.

245 IPR: Paper 72 at 4; EX2030 (PI Decision) at 22 and 51.

Even if "Consisting of" Modifies "Composition," Not Ocular Drop, ...

It still leads to the same construction—*single step, single drop*

- Petitioners admit the ***subject*** of what the single step administers is "***an*** ocular drop."
  - the eyedrop embodies the "composition"
- Petitioners admit claim 1 is "limited to administration of a ***single*** composition… in the form of an ocular drop"
  - Reply at 2, emphasis added
- Administering a ***single*** composition formulated as an eye drop, is still administering just one drop.
- Administering two drops constitutes administering two compositions, albeit of the same makeup.

245 IPR: Paper 72 at 2-3.

Petitioners' Expert Repeatedly Agree the Subject of the Administration Step is an Eyedrop



John Galanis, MD, FASC
(Petitioners' Expert)

> 54. I understand from counsel that, generally speaking, the first "consisting of" limits the steps of the method of reducing eye redness to the single step of topically administering an ocular drop, and the second "consisting of" limits the

> 55. The '245 patent prosecution history supports my understanding that the "consisting of" phrases limit the method of claim 1 to the single step of topically administering an ocular drop that contains brimonidine as the sole active ingredient in the ocular drop. During prosecution, the applicant stated that, as modified by the

245 IPR: EX1014 (Galanis Decl.) at ¶¶ 54-55

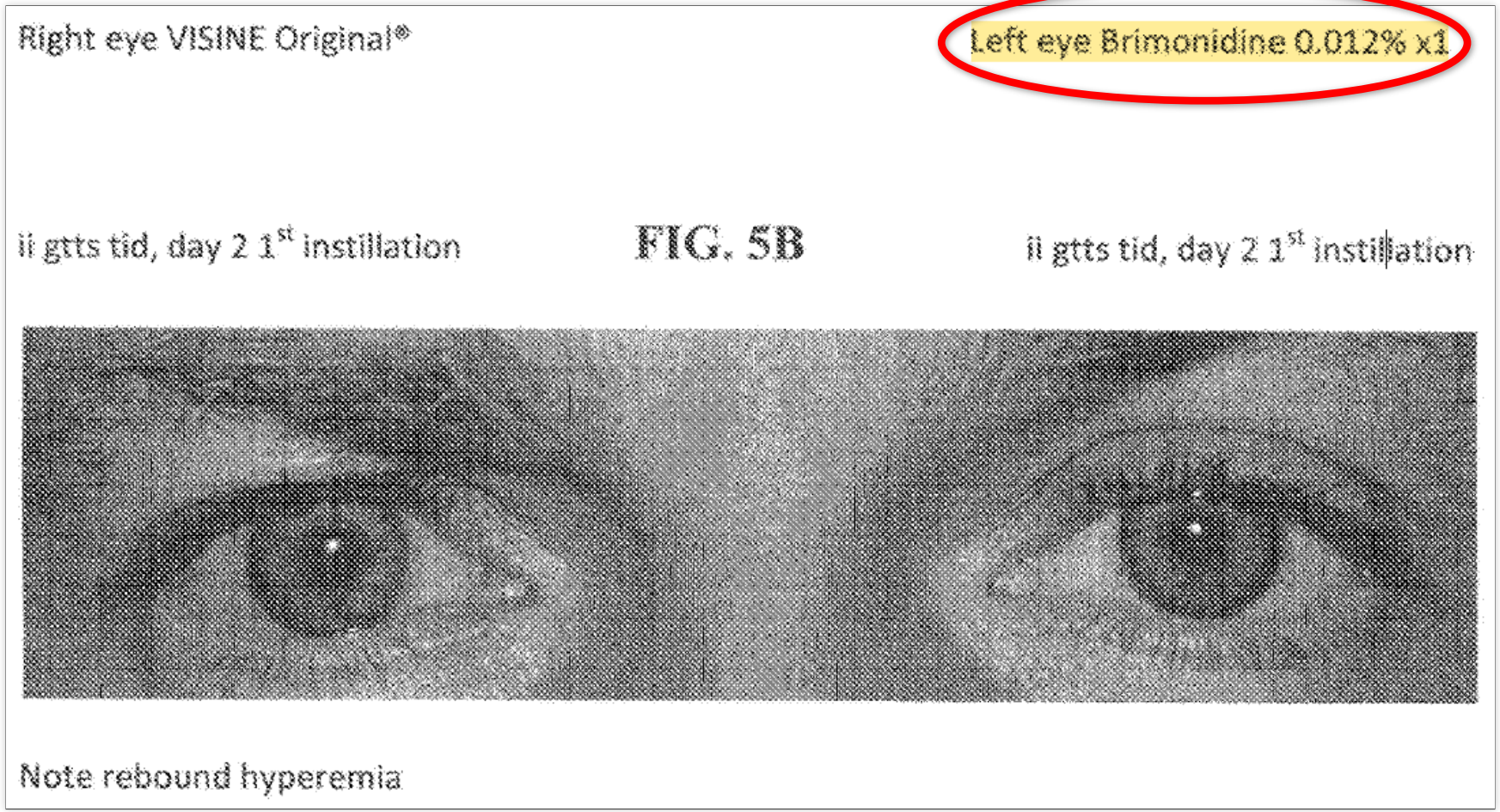
Patent Owner's Construction Naturally Aligns with the Specification

"The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction."

Phillips v. AWH Corp., 415 F.3d 1303, 1316 (Fed. Cir. 2005), *citing Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)

245 IPR: Paper 25 at 13, Paper 72 at 8.

Experiment in Figs. 5A-5C Supports a Single Drop



- The specification teaches "ii gtts tid" intended to induce rebound hyperemia
- Brimonidine 0.012% x1 indicates a single drop

245 IPR: Paper 72 at 7-8; EX1001 at 3:49-55.

The Specification's Examples Support Patent Owner's Construction

- Example 1 – Three separate experiments of a single drop of low-dose brimonidine compared to prior commercial redness relievers
  - 245 IPR: EX1001 ('245 Patent) at FIGS. 4A-4D, EX1001 ('245 Patent) at 3:25-46
- Example 2 – Explicitly discloses the administration of one or two drops
  - 245 IPR: EX1001 ('245 Patent) at 21:31-36 (Example 2), EX2279 (Galanis Dep. Tr.) at 25:9-25
- Example 4 – Administers a single dose of brimonidine at 0.018%
  - 245 IPR: EX1001 ('245 Patent) at 21:61-22:10, EX1044 (Donnenfeld Dep. Tr.) 31:11-32:3
- Figures 5A-5C – Additional support for a single drop administration

Single Step, Single Drop Construction Applied Consistently

Nexus

- **Lumify's** label discloses a dosing regimen of only one drop of 0.025% brimonidine
  - Works in one minute, lasts for 8 hours
  - Subsequent treatments in a day are ***optional***

Validity

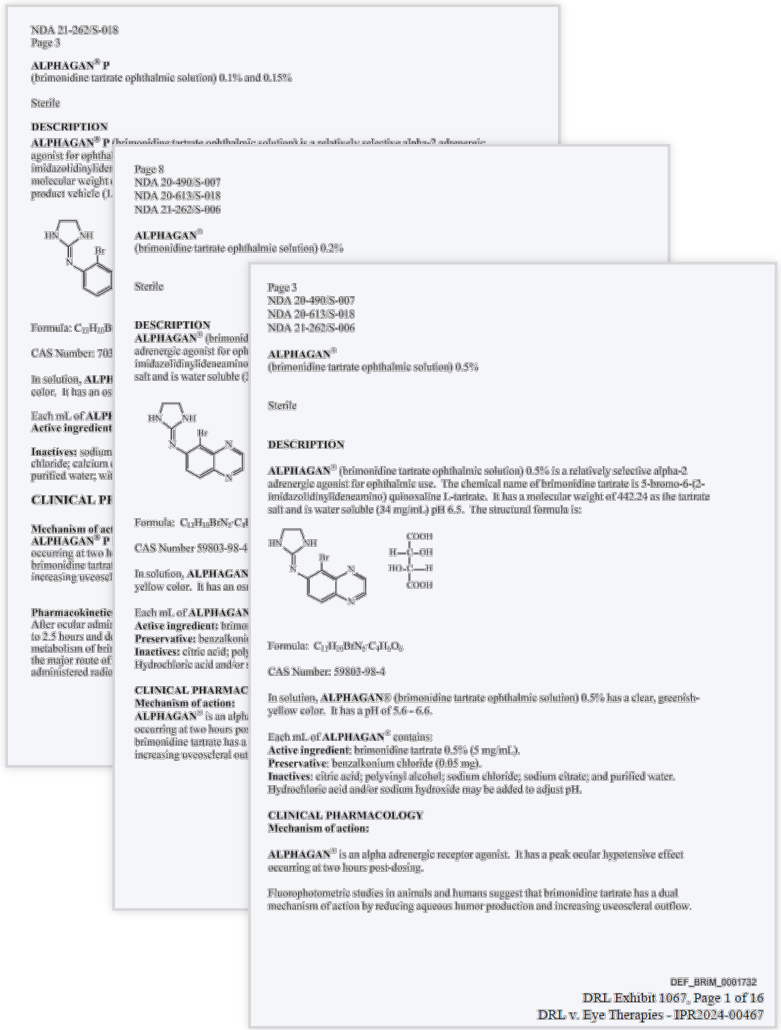
- **Gil Example 1** to achieve the effect of pain reduction from surgery discloses a dose loading regimen of 6-7 drops of 0.03% brimonidine → 0.2% just before surgery
  - 6-7 drop dosing regimen is ***not optional*** but required

245 IPR: Paper 72 at 9-10.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Clinical Studies of the Alphagan Products Would Have Been Highly Relevant and Reliable to a POSA Seeking to Develop a Redness Reliever

Highly Relevant and Reliable Alphagan Trials


NDA 21-262/S-018
Page 3

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

Page 8
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

Page 3
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL) pH 6.5. The structural formula is:

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.5% has a clear, greenish-yellow color. It has a pH of 5.6 - 6.6.

Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate 0.5% (5 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY
Mechanism of action:

ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

DEF_BRIM_0001732
DRL Exhibit 1067, Page 1 of 16
DRL v. Eye Therapies - IPR2024-00467

- Multiple human clinical studies with brimonidine, at various doses.

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

EX1067 at 1 (Alphagan 0.5% Label 2001)

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

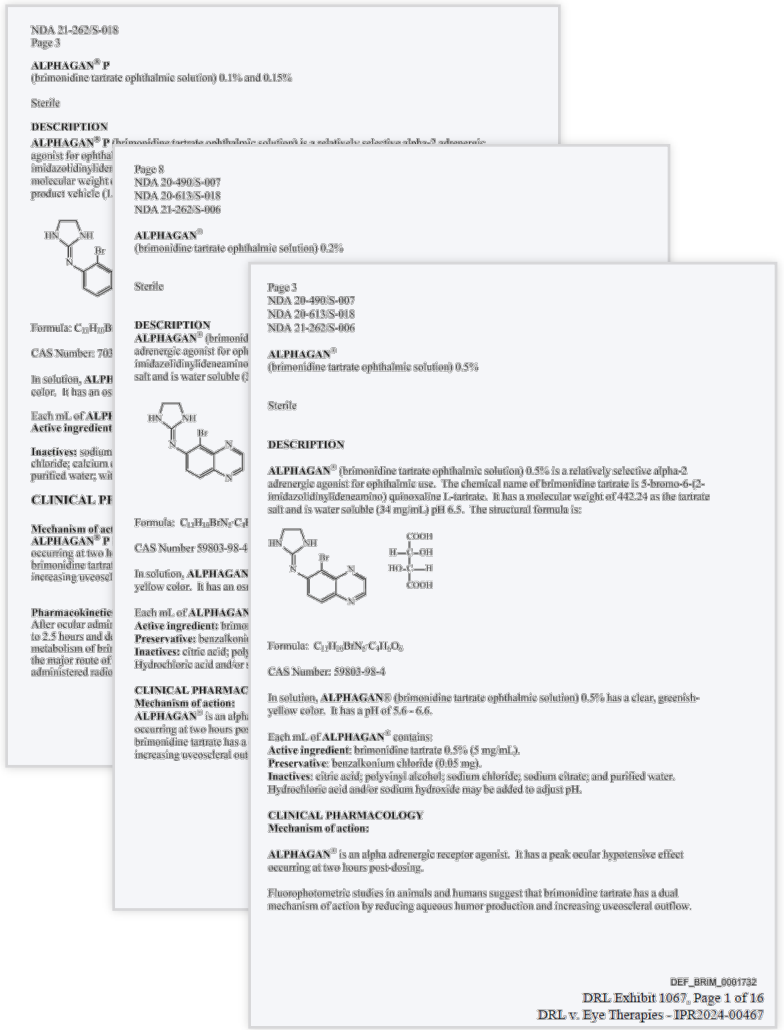
EX1067 at 6 (Alphagan 0.2% Label 2001)

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

EX1068 at 1 (Alphagan P Label 2005)

245 IPR: Paper 25 at 48, Paper 72 at 10;
600 IPR: Paper 21 at 42, Paper 68 at 2-3.

Alphagan Trials' Observed "Conjunctival Blanching" Would Have Been Highly Relevant to a POSA



NDA 21-262/S-018
Page 3

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

Page 8
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

Page 3
NDA 20-490/S-007
NDA 20-613/S-018
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(brimonidine tartrate ophthalmic solution) 0.5%

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ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

DEF_BRIM_0001732
DRL Exhibit 1067, Page 1 of 16
DRL v. Eye Therapies - IPR2024-00467

- Conjunctival blanching was reported as an adverse event with 0.5% and 0.2% brimonidine

Alphagan® 0.5%

ADVERSE REACTIONS

The most common adverse events reported in association with the use of **ALPHAGAN®** 0.5% in conjunction with ALT was transient conjunctival blanching in 50% of patients and upper lid retraction in 30% of patients.

EX1067 at 4 (Alphagan 0.5% Label 2001)

Alphagan® 0.2%

ADVERSE REACTIONS

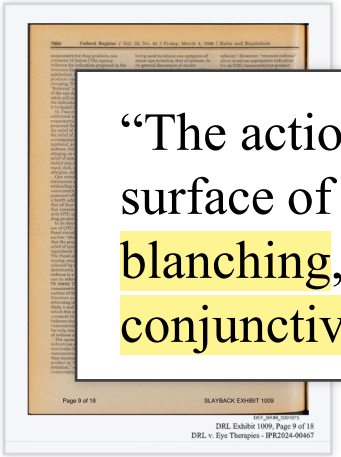
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Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

EX1067 at 9 (Alphagan 0.2% Label 2001)

245 IPR: Paper 25 at 41-48, Paper 72 at 12-14;
600 IPR: Paper 21 at 35-42, Paper 68 at 4-6.

POSAs Understood "Conjunctival Blanching" Meant Whitening of Conjunctiva and Reduction in Redness



"The action of a vasoconstrictor when applied to the surface of the eye is described in the literature as blanching, bleaching, and whitening of reddened conjunctiva (Refs. 1 and 2)."

EX1009 (Federal Register) at 9

- FDA's monograph for OTC ophthalmic drugs
  - supports that the Alphagan labels' reference to conjunctival blanching meant conjunctival whitening / redness reduction.



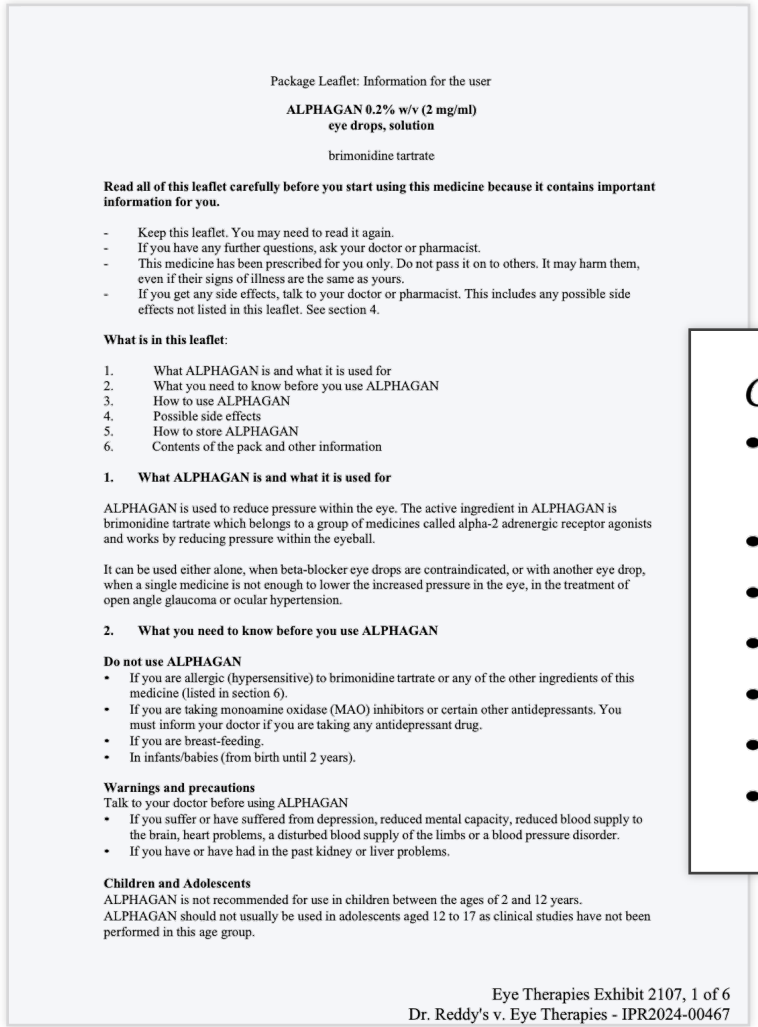
Dr. Robert Noecker
(Patentee's expert)

whitening of reddened conjunctiva." EX-1009, Federal Register 1988 at 9. In my opinion, a POSA would have understood this statement to describe blanching as the method by which a redness reliever whitens the conjunctiva, assuming sufficient vasoconstriction to achieve blanching/whitening of the eye. The '245 patent uses

245 IPR: EX2223 (Noecker Decl.) at ¶189; 600 IPR: EX2223 (Noecker Decl.) at ¶ 184

245 IPR: Paper 25 at 42-44, Paper 72 at 12;
600 IPR: Paper 21 at 36-38, Paper 68 at 4.

POSAs Understood "Conjunctival Blanching" Meant Whitening of Conjunctiva and Reduction in Redness



Package Leaflet: Information for the user

ALPHAGAN 0.2% w/v (2 mg/ml)
eye drops, solution

brimonidine tartrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What ALPHAGAN is and what it is used for
2. What you need to know before you use ALPHAGAN
3. How to use ALPHAGAN
4. Possible side effects
5. How to store ALPHAGAN
6. Contents of the pack and other information

1. What ALPHAGAN is and what it is used for

ALPHAGAN is used to reduce pressure within the eye. The active ingredient in ALPHAGAN is brimonidine tartrate which belongs to a group of medicines called alpha-2 adrenergic receptor agonists and works by reducing pressure within the eyeball.

It can be used either alone, when beta-blocker eye drops are contraindicated, or with another eye drop, when a single medicine is not enough to lower the increased pressure in the eye, in the treatment of open angle glaucoma or ocular hypertension.

2. What you need to know before you use ALPHAGAN

Do not use ALPHAGAN
- If you are allergic (hypersensitive) to brimonidine tartrate or any of the other ingredients of this medicine (listed in section 6).
- If you are taking monoamine oxidase (MAO) inhibitors or certain other antidepressants. You must inform your doctor if you are taking any antidepressant drug.
- If you are breast-feeding.
- In infants/babies (from birth until 2 years).

Warnings and precautions
Talk to your doctor before using ALPHAGAN
- If you suffer or have suffered from depression, reduced mental capacity, reduced blood supply to the brain, heart problems, a disturbed blood supply of the limbs or a blood pressure disorder.
- If you have or have had in the past kidney or liver problems.

Children and Adolescents
ALPHAGAN is not recommended for use in children between the ages of 2 and 12 years.
ALPHAGAN should not usually be used in adolescents aged 12 to 17 as clinical studies have not been performed in this age group.

Eye Therapies Exhibit 2107, 1 of 6
Dr. Reddy's v. Eye Therapies - IPR2024-00467

- Corroborated by Alphagan 0.2% Package Leaflet

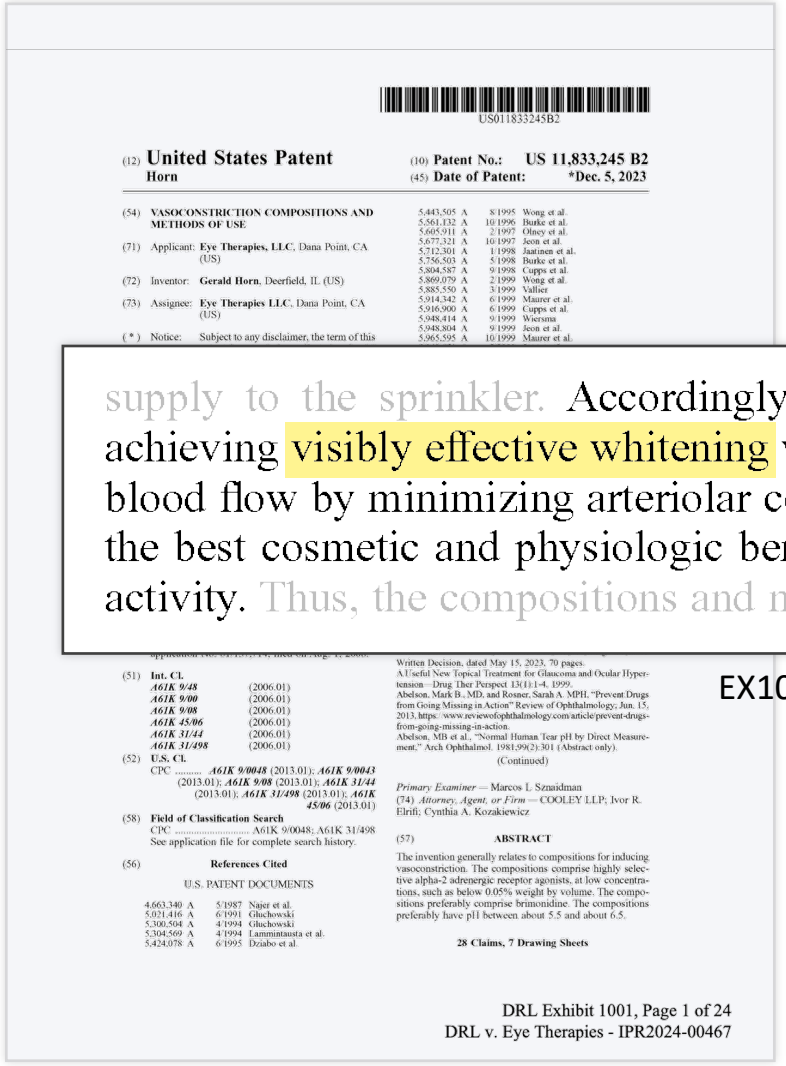
Common (may affect up to 1 in 10 people):

- Local irritation (inflammation and swelling of the eyelid, swelling of the see-through layer which covers the surface of the eye, sticky eyes, pain and tearing)
- Sensitivity to light
- Erosion on the surface of the eye and staining
- Eye dryness
- Whitening of the see-through layer which covers the surface of the eye
- Abnormal vision
- Inflammation of the see-through layer which covers the surface of the eye

EX2107 (Alphagan Package Leaflet) at 4

245 IPR: Paper 25 at 43, Paper 72 at 12;
600 IPR: Paper 21 at 37, Paper 68 at 4.

Consistent with Teaching in the ’245 Patent Specification Touting Superior Whitening Effects of Invention



US011833245B2

(12) **United States Patent**
Horn

(10) **Patent No.: US 11,833,245 B2**
(45) **Date of Patent: *Dec. 5, 2023**

(54) **VASOCONSTRICTION COMPOSITIONS AND METHODS OF USE**

(71) Applicant: **Eye Therapies, LLC**, Dana Point, CA (US)

(72) Inventor: **Gerald Horn**, Deerfield, IL (US)

(73) Assignee: **Eye Therapies LLC**, Dana Point, CA (US)

(*) Notice: Subject to any disclaimer, the term of this

supply to the sprinkler. Accordingly, this method allows achieving visibly effective whitening while optimizing total blood flow by minimizing arteriolar constriction to produce the best cosmetic and physiologic benefits of decongestant activity. Thus, the compositions and methods of the present

(51) **Int. Cl.**
A61K 9/48 (2006.01)
A61K 9/00 (2006.01)
A61K 9/08 (2006.01)
A61K 45/06 (2006.01)
A61K 31/44 (2006.01)
A61K 31/498 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 9/0048*** (2013.01); ***A61K 9/0043*** (2013.01); ***A61K 9/08*** (2013.01); ***A61K 31/44*** (2013.01); ***A61K 31/498*** (2013.01); ***A61K 45/06*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 9/0048; A61K 31/498
See application file for complete search history.

(56) **References Cited**

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A Useful New Topical Treatment for Glaucoma and Ocular Hypertension—Drug Ther Perspect 13(1):1-4, 1999.
Abelson, Mark B., MD, and Rosner, Sarah A. MPH, "Prevent Drugs from Going Missing in Action" Review of Ophthalmology, Jun. 15, 2013, https://www.reviewofophthalmology.com/article/prevent-drugs-from-going-missing-in-action.
Abelson, MB et al., "Normal Human Tear pH by Direct Measurement," Arch Ophthalmol. 1981;99(2):301 (Abstract only).
(Continued)

Primary Examiner — Marcos L Sznaidman
(74) *Attorney, Agent, or Firm* — COOLEY LLP; Ivor R. Elrifi; Cynthia A. Kozakiewicz

(57) **ABSTRACT**

The invention generally relates to compositions for inducing vasoconstriction. The compositions comprise highly selective alpha-2 adrenergic receptor agonists, at low concentrations, such as below 0.05% weight by volume. The compositions preferably comprise brimonidine. The compositions preferably have pH between about 5.5 and about 6.5.

28 Claims, 7 Drawing Sheets

DRL Exhibit 1001, Page 1 of 24
DRL v. Eye Therapies - IPR2024-00467

EX1001 (’245 Patent) at 6:63-67

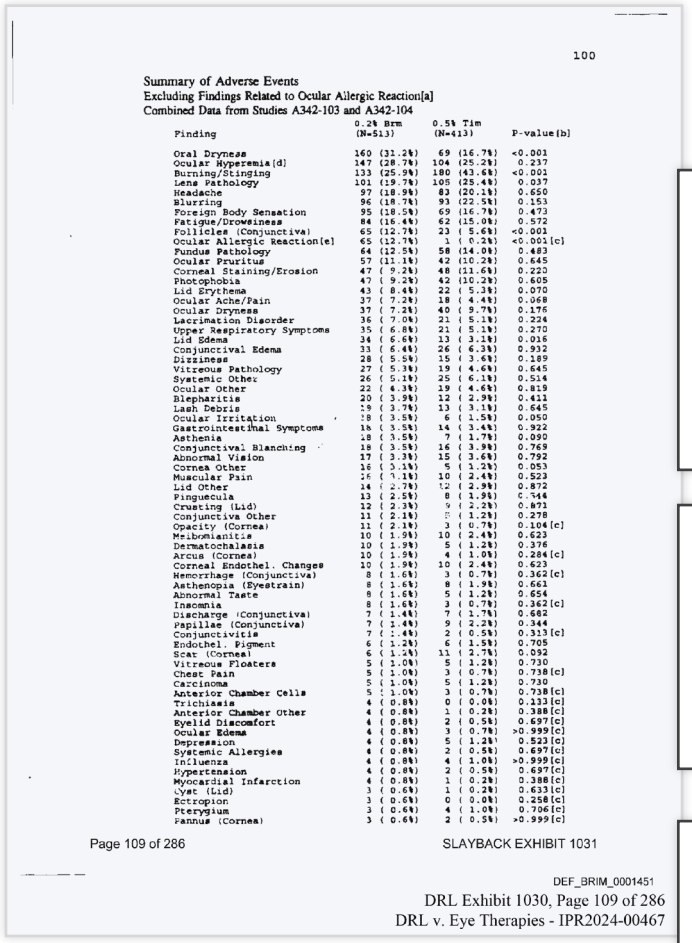
In a preferred embodiment, the invention generally relates to a method of scleral whitening without significant rebound hyperemia, comprising administering to a patient in need thereof a topical composition comprising a selective a-2 adrenergic receptor agonist having a binding affinity of 100 fold or greater for a-2 over a-1 adrenergic receptors, or a pharmaceutically acceptable salt thereof, wherein said selective a-2 adrenergic receptor agonist is present at a concentration below about 0.06% weight by volume.

EX1001 (’245 Patent) at 14:23-31

This method allows achieving a more effective scleral whitening (i.e., whiter shades of scleral color) than possible with prior art compositions and methods, as a result of more effective vasoconstriction that creates sufficient constriction of the capillary bed within the sclera to induce an overall whitening not observed with prior art, allowing for an improved cosmetic appearance.

EX1001 (’245 Patent) at 14:32-38

Though Not Endpoint of Alphagan Studies, Conjunctival Blanching Data was Still Collected and Statistically Analyzed



100

Summary of Adverse Events
Excluding Findings Related to Ocular Allergic Reaction[a]
Combined Data from Studies A342-103 and A342-104

Finding	0.2% Brm (N=513)	0.5% Tim (N=413)	P-value[b]
Oral Dryness	160 (31.2%)	69 (16.7%)	<0.001
Ocular Hyperemia[d]	147 (28.7%)	104 (25.2%)	0.237
Burning/Stinging	133 (25.9%)	180 (43.6%)	<0.001
Lens Pathology	101 (19.7%)	105 (25.4%)	0.037
Headache	97 (18.9%)	83 (20.1%)	0.650
Blurring	96 (18.7%)	93 (22.5%)	0.153
Foreign Body Sensation	95 (18.5%)	69 (16.7%)	0.473
Fatigue/Drowsiness	84 (16.4%)	62 (15.0%)	0.572
Follicles (Conjunctiva)	65 (12.7%)	23 (5.6%)	<0.001
Ocular Allergic Reaction[e]	65 (12.7%)	1 (0.2%)	<0.001[c]
Fundus Pathology	64 (12.5%)	58 (14.0%)	0.483
Ocular Pruritus	57 (11.1%)	42 (10.2%)	0.645
Corneal Staining/Erosion	47 (9.2%)	48 (11.6%)	0.220
Photophobia	47 (9.2%)	42 (10.2%)	0.605
Lid Erythema	43 (8.4%)	22 (5.3%)	0.070
Ocular Ache/Pain	37 (7.2%)	18 (4.4%)	0.068
Ocular Dryness	37 (7.2%)	40 (9.7%)	0.176
Lacrimation Disorder	36 (7.0%)	21 (5.1%)	0.224
Upper Respiratory Symptoms	35 (6.8%)	21 (5.1%)	0.270
Lid Edema	34 (6.6%)	13 (3.1%)	0.016
Conjunctival Edema	33 (6.4%)	26 (6.3%)	0.932
Dizziness	28 (5.5%)	15 (3.6%)	0.189
Vitreous Pathology	27 (5.3%)	19 (4.6%)	0.645
Systemic Other	26 (5.1%)	25 (6.1%)	0.514
Ocular Other	22 (4.3%)	19 (4.6%)	0.819
Blepharitis	20 (3.9%)	12 (2.9%)	0.421
Lash Debris	19 (3.7%)	13 (3.1%)	0.645
Ocular Irritation	18 (3.5%)	6 (1.5%)	0.050
Gastrointestinal Symptoms	18 (3.5%)	14 (3.4%)	0.922
Asthenia	18 (3.5%)	7 (1.7%)	0.090
Conjunctival Blanching	18 (3.5%)	16 (3.9%)	0.769
Abnormal Vision	17 (3.3%)	15 (3.6%)	0.792
Cornea Other	16 (3.1%)	5 (1.2%)	0.053
Muscular Pain	15 (2.9%)	10 (2.4%)	0.523
Lid Other	14 (2.7%)	12 (2.9%)	0.872
Pinguecula	13 (2.5%)	8 (1.9%)	0.544
Crusting (Lid)	12 (2.3%)	9 (2.2%)	0.873
Conjunctiva Other	11 (2.1%)	5 (1.2%)	0.278
Opacity (Cornea)	11 (2.1%)	3 (0.7%)	0.104[c]
Meibomianitis	10 (1.9%)	10 (2.4%)	0.623
Dermatochalasis	10 (1.9%)	5 (1.2%)	0.376
Arcus (Cornea)	10 (1.9%)	4 (1.0%)	0.284[c]
Corneal Endothel. Changes	10 (1.9%)	10 (2.4%)	0.623
Hemorrhage (Conjunctiva)	8 (1.6%)	3 (0.7%)	0.362[c]
Asthenopia (Eyestrain)	8 (1.6%)	8 (1.9%)	0.661
Abnormal Taste	8 (1.6%)	5 (1.2%)	0.654
Insomnia	8 (1.6%)	3 (0.7%)	0.362[c]
Discharge (Conjunctiva)	7 (1.4%)	7 (1.7%)	0.682
Papillae (Conjunctiva)	7 (1.4%)	9 (2.2%)	0.344
Conjunctivitis	7 (1.4%)	2 (0.5%)	0.313[c]
Endothel. Pigment	6 (1.2%)	6 (1.5%)	0.705
Scar (Cornea)	6 (1.2%)	11 (2.7%)	0.092
Vitreous Floaters	5 (1.0%)	5 (1.2%)	0.730
Chest Pain	5 (1.0%)	3 (0.7%)	0.738[c]
Carcinoma	5 (1.0%)	5 (1.2%)	0.730
Anterior Chamber Cells	5 (1.0%)	3 (0.7%)	0.738[c]
Trichiasis	4 (0.8%)	0 (0.0%)	0.133[c]
Anterior Chamber Other	4 (0.8%)	1 (0.2%)	0.388[c]
Eyelid Discomfort	4 (0.8%)	2 (0.5%)	0.697[c]
Ocular Edema	4 (0.8%)	3 (0.7%)	>0.999[c]
Depression	4 (0.8%)	5 (1.2%)	0.523[c]
Systemic Allergies	4 (0.8%)	2 (0.5%)	0.697[c]
Influenza	4 (0.8%)	4 (1.0%)	>0.999[c]
Hypertension	4 (0.8%)	2 (0.5%)	0.697[c]
Myocardial Infarction	4 (0.8%)	1 (0.2%)	0.388[c]
Cyst (Lid)	3 (0.6%)	1 (0.2%)	0.633[c]
Ectropion	3 (0.6%)	0 (0.0%)	0.258[c]
Pterygium	3 (0.6%)	4 (1.0%)	0.706[c]
Pannus (Cornea)	3 (0.6%)	2 (0.5%)	>0.999[c]

Page 109 of 286

SLAYBACK EXHIBIT 1031

DEF_BRIM_0001451

DRL Exhibit 1030, Page 109 of 286
DRL v. Eye Therapies - IPR2024-00467

- Blanching data was collected and indisputably statistically analyzed making them highly relevant to a POSA

Summary of Adverse Events
Excluding Findings Related to Ocular Allergic Reaction[a]
Combined Data from Studies A342-103 and A342-104

Finding	0.2% Brm (N=513)	0.5% Tim (N=413)	P-value[b]
***			
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Conjunctival Blanching	18 (3.5%)	16 (3.9%)	0.769
Abnormal Vision	17 (3.3%)	15 (3.6%)	0.792
Cornea Other	16 (3.1%)	5 (1.2%)	0.053
***			

[b] Unless stated otherwise, p-value based on Pearson's Chi-square test.

EX1030 (Alphagan NDA) at 109-111

245 IPR: Paper 25 at 47-48, Paper 72 at 14-15;
600 IPR: Paper 21 at 41-42, paper 68 at 6-7.

Adverse Event Does Not Mean Undesirable for Any Purpose

- A POSA would not have been dissuaded from considering the statistically-analyzed conjunctival blanching data.

  – Any event affecting the ocular surface would have been reported as "adverse."

  EX2019 (Stamer Tr.) at 81:8-19

  – Conjunctival blanching was not a serious adverse effect.

  EX1030 (Alphagan NDA) at 55

  – No patient withdrew from the study because of conjunctival blanching.

  EX1030 (Alphagan NDA) at 129

245 IPR: Paper 25 at 47, Paper 72 at 13;
600 IPR: Paper 21 at 41, Paper 68 at 5.

Adverse Event Does Not Mean Undesirable for Any Purpose



Dr. Daniel W. Gil
(Patentee's expert)

Q. Why did you cite to Page 51 of the declaration – of [the Alphagan NDA]?

A. So this is reporting on adverse events that resulted in termination. And there's no reports of blanching having contributed to termination from the study, which would, again, indicate that when there were reports of blanching, it would not have been so severe to cause the investigator to terminate the patient from the study.

It would have probably been more in the range of – they would have been in the range of, you know, mild to moderate, which is really – you know, that would be in the terms of, if you were going after a hyperemia – a reduction of a hyperemia indication, that's what you would want to be targeting.

EX2280 (Gil IPR Tr.) 59:4-59:20

245 IPR: Paper 72 at 13; 600 IPR: Paper 68 at 5.

Alphagan's Conjunctival Blanching Data Carried an Imprimatur of High-Reliability



Mr. Kurt Karst
(Patentee's expert)

UNREBUTTED

67. With respect to Section 6 (Adverse Reactions), FDA's regulations state:

> This section must describe the overall adverse reaction profile of the drug based on the entire safety database. For
>
> ***
>
> (i) *Listing of adverse reactions.* This section must list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. The list or lists must be

245 IPR: EX2228 (Karst Decl.) at ¶67

94. The required inclusion of adverse reaction information in a particular drug product's Prescribing Information provides indicia of truthfulness and reliability. Not only are adverse reactions included in a drug product's Prescribing

EX2228 (Karst Decl.) at ¶94

245 IPR: Paper 25 at 44, Paper 72 at 14-17;
600 IPR: Paper 21 at 38-39; Paper 68 at 6-9.

Conjunctival Blanching was Monitored and Recorded if Observed in All Alphagan Clinical Trials

Dr. Noecker was the only expert involved in Alphagan clinical trials



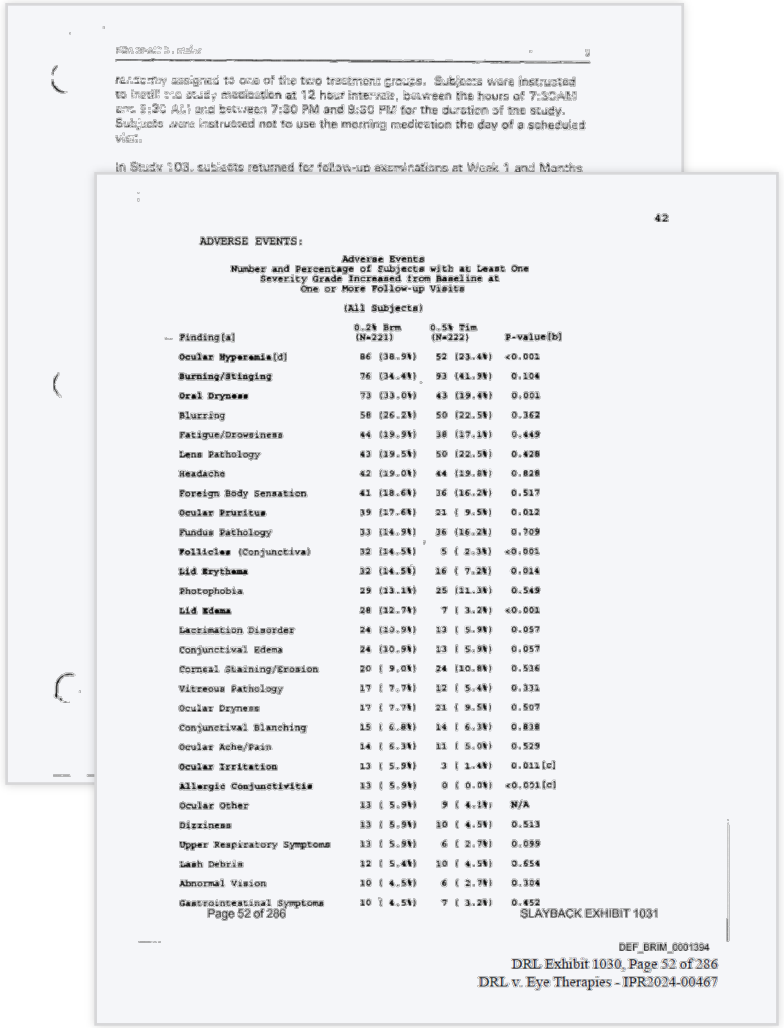
Dr. Robert Noecker
(Patentee's expert)

193. Once an ocular surface event is observed for a drug in a clinical trial, it will be recorded and monitored going forward, even in future trials of the drug at different concentrations. EX-2008, Dana Jan. 12, 2024 Dep. Tr. at 116:13-117:15. I

245 IPR: EX2223 (Noecker Decl.) at ¶193 (245 IPR); 600 IPR: EX2223 (Noecker Decl.) at ¶188

245 IPR: Paper 25 at 44, Paper 72 at 14;
600 IPR: Paper 21 at 38, Paper 68 at 6.

Conjunctival Blanching was Monitored and Recorded in Alphagan Trials Based on Protocol Making the Data Highly Reliable



randomly assigned to one of the two treatment groups. Subjects were instructed to instill the study medication at 12 hour intervals, between the hours of 7:30AM and 8:30 AM and between 7:30 PM and 8:30 PM for the duration of the study. Subjects were instructed not to use the morning medication the day of a scheduled visit.

In Study 103, subjects returned for follow-up examinations at Week 1 and Months

42

ADVERSE EVENTS:

Adverse Events
Number and Percentage of Subjects with at Least One Severity Grade Increased from Baseline at One or More Follow-up Visits
(All Subjects)

Finding[a]	0.2% Brm (N=221)	0.5% Tim (N=222)	P-value[b]
Ocular Hyperemia[d]	86 (38.9%)	52 (23.4%)	<0.001
Burning/Stinging	76 (34.4%)	93 (41.9%)	0.104
Oral Dryness	73 (33.0%)	43 (19.4%)	0.001
Blurring	58 (26.2%)	50 (22.5%)	0.362
Fatigue/Drowsiness	44 (19.9%)	38 (17.1%)	0.449
Lens Pathology	43 (19.5%)	50 (22.5%)	0.428
Headache	42 (19.0%)	44 (19.8%)	0.828
Foreign Body Sensation	41 (18.6%)	36 (16.2%)	0.517
Ocular Pruritus	39 (17.6%)	21 (9.5%)	0.012
Fundus Pathology	33 (14.9%)	36 (16.2%)	0.709
Follicles (Conjunctiva)	32 (14.5%)	5 (2.3%)	<0.001
Lid Erythema	32 (14.5%)	16 (7.2%)	0.014
Photophobia	29 (13.1%)	25 (11.3%)	0.549
Lid Edema	28 (12.7%)	7 (3.2%)	<0.001
Lacrimation Disorder	24 (10.9%)	13 (5.9%)	0.057
Conjunctival Edema	24 (10.9%)	13 (5.9%)	0.057
Corneal Staining/Erosion	20 (9.0%)	24 (10.8%)	0.536
Vitreous Pathology	17 (7.7%)	12 (5.4%)	0.331
Ocular Dryness	17 (7.7%)	21 (9.5%)	0.507
Conjunctival Blanching	15 (6.8%)	14 (6.3%)	0.838
Ocular Ache/Pain	14 (6.3%)	11 (5.0%)	0.529
Ocular Irritation	13 (5.9%)	3 (1.4%)	0.011[c]
Allergic Conjunctivitis	13 (5.9%)	0 (0.0%)	<0.001[c]
Ocular Other	13 (5.9%)	9 (4.1%)	N/A
Dizziness	13 (5.9%)	10 (4.5%)	0.513
Upper Respiratory Symptoms	13 (5.9%)	6 (2.7%)	0.099
Lash Debris	12 (5.4%)	10 (4.5%)	0.654
Abnormal Vision	10 (4.5%)	6 (2.7%)	0.304
Gastrointestinal Symptoms	10 (4.5%)	7 (3.2%)	0.452

Page 52 of 286

SLAYBACK EXHIBIT 1031

DEF_BRIM_0001394

DRL Exhibit 1030, Page 52 of 286
DRL v. Eye Therapies - IPR2024-00467

- Alphagan NDA confirms protocol used:

ADVERSE EVENTS:

Adverse Events
Number and Percentage of Subjects with at Least One Severity Grade Increased from Baseline at One or More Follow-up Visits
(All Subjects)

Finding[a]	0.2% Brm (N=221)	0.5% Tim (N=222)	P-value[b]

EX1030 (Alphagan NDA) at 52

"Throughout the study, subjects were monitored for signs and symptoms of adverse events…. Any adverse event occurring during the study was recorded by the investigator, graded for severity (trace, mild, moderate, or severe), and assessed for relationship to the study treatment."

EX1030 (Alphagan NDA) at 119

245 IPR: Paper 25 at 47, Paper 72 at 15;
600 IPR: Paper 21 at 41, Paper 68 at 7.

Protocol Used for Monitoring and Reporting Conjunctival Blanching, if Observed, Led to Consistency and Reliability



Dr. Reza Dana
(Petitioners' expert)

Q. Yeah. Is it fair to say that what these protocols that are being developed by the clinical investigators in conjunction with the sponsors, for example, that they lead to consistency and reliability ultimately in reporting the results of the various metrics, whether they be efficacy or side effects, metrics?

A. Yes. I would generally agree with that.

EX2008 (Dana PI Dep. Tr.) at 114:3-13 (objections omitted)

Alphagan's Conjunctival Blanching Data, or Lack of Data, Carried an Imprimatur of High-Reliability

- FDA thoroughly considered the adverse event data and deemed them sufficiently well-supported and found no issues with the values reported on the Alphagan and Alphagan P labels.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects, including adequate demographic subsets, were exposed to the drug product in a well-controlled, randomized, clinical trial. The doses and durations of exposure were adequate to assess safety for the intended use.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The applicant's evaluation of potential adverse effects for this pharmacological class of drug is adequate.

7.2.8 Assessment of Quality and Completeness of Data

The submitted safety database appeared adequate and complete for the class of pharmacologic class of agents.

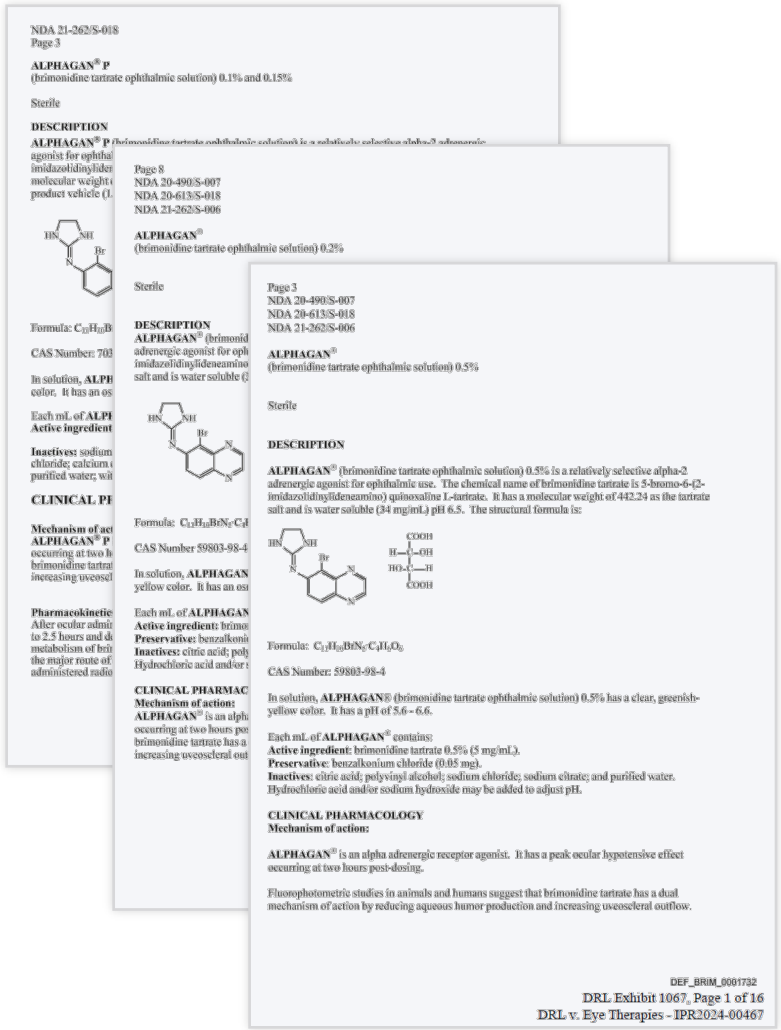
EX1075 (Medical Review NDA) at 63

245 IPR: Paper 25 at 46-47, Paper 72 at 15-16;
600 IPR: Paper 21 at 40-41, Paper 68 at 7-8.

Alphagan Clinical Studies Established the Minimum Effective Redness-Relieving Dose of Brimonidine Was About 0.2%

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

A Dose Related Response was Observed for "Conjunctival Blanching" in the Alphagan Clinical Studies



NDA 21-262/S-018
Page 3

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

Page 8
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

Page 3
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is a relatively selective alpha-2 adrenergic agonist for ophthalmic use. The chemical name of brimonidine tartrate is 5-bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular weight of 442.24 as the tartrate salt and is water soluble (34 mg/mL) pH 6.5. The structural formula is:

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.5% has a clear, greenish-yellow color. It has a pH of 5.6 - 6.6.

Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate 0.5% (5 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate; and purified water. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY
Mechanism of action:

ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocular hypotensive effect occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidine tartrate has a dual mechanism of action by reducing aqueous humor production and increasing uveoscleral outflow.

DEF_BRIM_0001732
DRL Exhibit 1067, Page 1 of 16
DRL v. Eye Therapies - IPR2024-00467

Alphagan® 0.5%

ADVERSE REACTIONS

The most common adverse events reported in association with the use of **ALPHAGAN®** 0.5% in conjunction with ALT was transient conjunctival blanching in 50% of patients and upper lid retraction in 30% of patients.

EX1067 at 4 (Alphagan 0.5% Label 2001)

Alphagan® 0.2%

ADVERSE REACTIONS

***

Events occurring in approximately 3-9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

EX1067 at 9 (Alphagan 0.2% Label 2001)

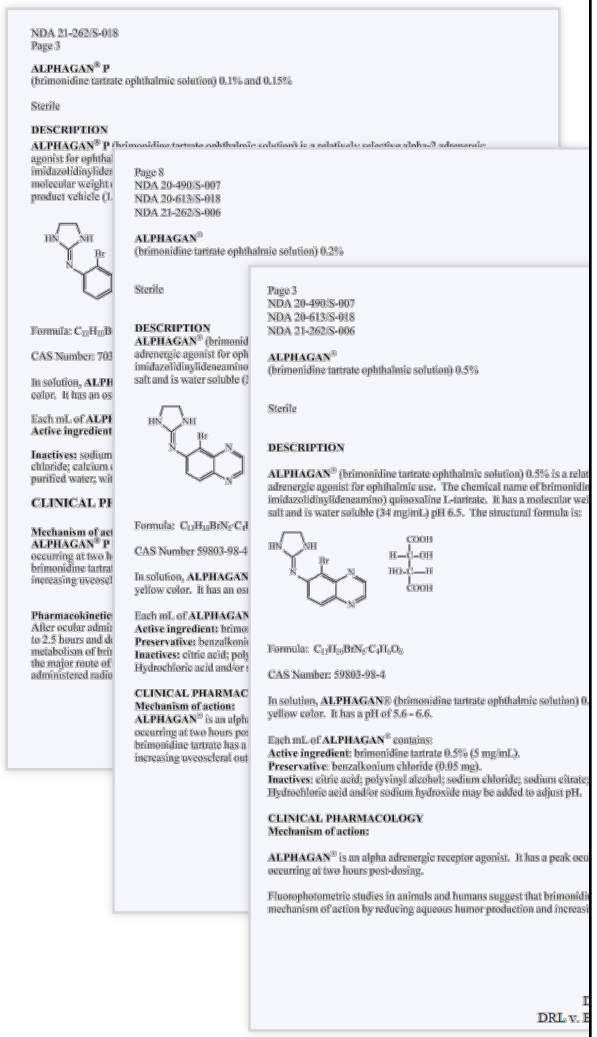
Alphagan® P 0.1 and 0.15%

- Conjunctival blanching **NOT** observed in any subjects!

EX1068 at 4 (Alphagan P Label 2005)

245 IPR: Paper 25 at 45 and 48, Paper 72 at 14 and 21;
600 IPR: Paper 21 at 39 and 42, Paper 68 at 6 and 13.

Alphagan Clinical Studies Established the Minimum Effective Redness-Relieving Dose of Brimonidine Was About 0.2%


NDA 21-262/S-018
Page 3

ALPHAGAN® P
(brimonidine tartrate ophthalmic solution) 0.1% and 0.15%

Sterile

DESCRIPTION

Page 8
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

Sterile

DESCRIPTION

Page 3
NDA 20-490/S-007
NDA 20-613/S-018
NDA 21-262/S-006

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

Sterile

DESCRIPTION

ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% is a relat
adrenergic agonist for ophthalmic use. The chemical name of brimonidi
imidazolidinylideneamino) quinoxaline L-tartrate. It has a molecular wei
salt and is water soluble (34 mg/mL) pH 6.5. The structural formula is:

Formula: $C_{11}H_{10}BrN_5 \cdot C_4H_6O_6$

CAS Number: 59803-98-4

In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.
yellow color. It has a pH of 5.6 - 6.6.

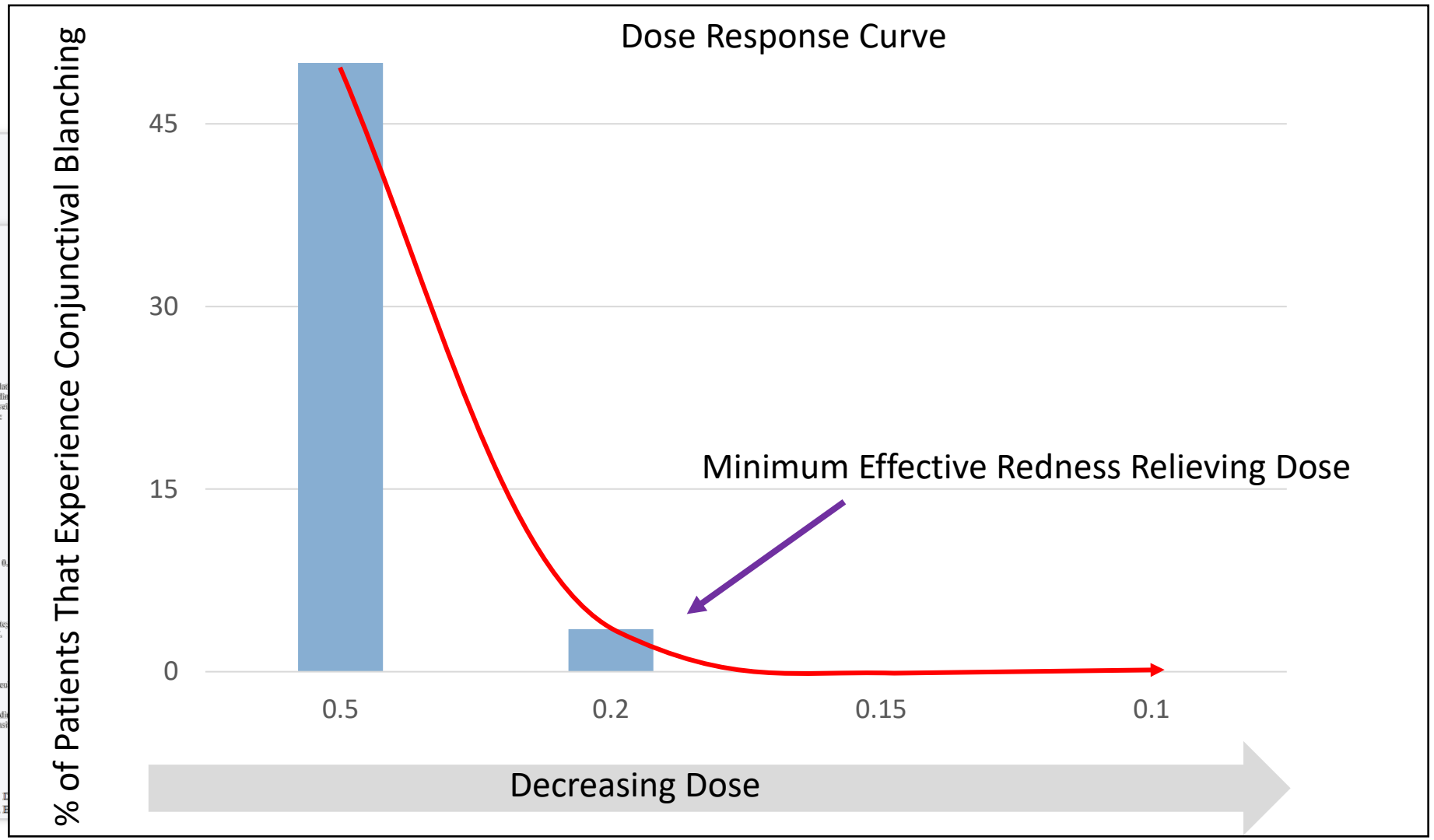
Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate 0.5% (5 mg/mL).
Preservative: benzalkonium chloride (0.05 mg).
Inactives: citric acid; polyvinyl alcohol; sodium chloride; sodium citrate;
Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

CLINICAL PHARMACOLOGY
Mechanism of action:

ALPHAGAN® is an alpha adrenergic receptor agonist. It has a peak ocu
occurring at two hours post-dosing.

Fluorophotometric studies in animals and humans suggest that brimonidi
mechanism of action by reducing aqueous humor production and increasi

DRL v. E



EX1067 (ALPHAGAN® Labels); EX1068 (ALPHAGAN® P Label)

245 IPR: Paper 25 at 45 and 48, Paper 72 at 14 and 20-21;
600 IPR: Paper 21 at 39 and 42, Paper 68 at 6 and 12-13.

Contemporaneous Real-World Evidence Guards Against Hindsight

Patent Owner Has Presented Testimony From Dr. Daniel W. Gil, Lead Inventor of the "Gil Patent" and an Expert in Alpha-Adrenergic Drugs



Dr. Daniel W. Gil
(Patentee's expert)

1. I, Daniel W. Gil, Ph.D., submit this declaration at the request of Patent Owner Eye Therapies, LLC ("Patent Owner") as the lead inventor on the "Gil patent," U.S. Patent No. 6,294,553 (EX-1004), entitled *Methods for Treating Ocular Pain*, based on my personal knowledge and as a person with particular expertise in drug discovery, drug repurposing, pharmacology and brimonidine. I understand this

EX2227 (Gil Decl.) at ¶ 1

in New York, focusing on neurogenetics. After that, I worked at Allergan in various positions (from Scientist/Senior Research Investigator to Vice President, Research Technologies and Portfolio) for over 30 years. I directed and oversaw teams of researchers in drug discovery, including in drug repurposing, pain, and drugs acting on alpha-adrenergic receptors. As part of my duties at Allergan, I gained extensive experience with the alpha-adrenergic drug brimonidine tartrate, the active ingredient

EX2227 (Gil Decl.) at ¶ 3

245 IPR: Paper 25 at 2; 600 IPR: Paper 21 at 2.

Allergan and Dr. Gil Actively Sought to Repurpose Brimonidine for New Therapeutic Uses



Dr. Daniel W. Gil
(Patentee's expert)

22. As part of my responsibility at Allergan, I worked with brimonidine in multiple types of projects. For example, Allergan investigated brimonidine for *ocular neovascularization* and *ocular pain* and filed patent applications on both methods of use. (*See, e.g.*, EX-1004, Gil patent; EX-2113, J. Kusari, et al., *Effect of Brimonidine on Retinal and Choroidal Neovascularization in a Mouse Model of Retinopathy of Prematurity and Laser-Treated Rats*, Invest. Ophthalmol. Vis. Sci. 52(8):5424-5431 (2011).) Allergan also published numerous articles about the use of brimonidine and posited future uses, for example in promoting retinal ganglion cell survival in glaucomatous neuropathy and in macular degeneration. (EX-2114,

EX2227 (Gil Decl.) at ¶ 22

245 IPR: Paper 25 at 2, 3, 19-20, Paper 72 at 21.
600 IPR: Paper 21 at 2, 3, 21, Paper 68 at 13.

Brimonidine Was Known to Cause Unwanted Side Effects, Including Eye Redness



Dr. Daniel W. Gil
(Patentee's expert)

> 51. Our findings would have provided the skilled scientist with yet another reason not to pursue brimonidine or other known α2 agonists as therapeutics. Specifically, in the AU '265 Application, we noted that agonists of the α2 receptors are commonly associated with undesirable side effects such as sedation and cardiovascular depression that would severely limit their ocular use. (EX-2118, AU

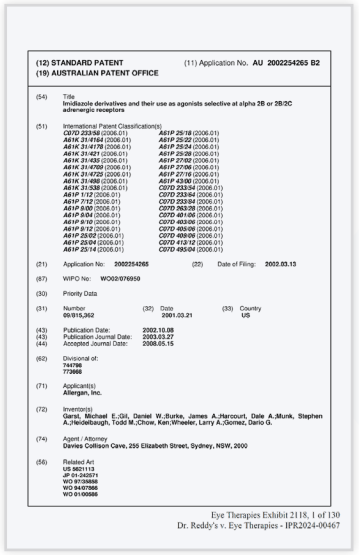
EX2227 (Gil Decl.) at ¶ 51

> researched in the field of ophthalmology by top companies for decades. It is also quite surprising because ALPHAGAN and ALPHAGAN P were generally known to ***cause*** redness, particularly at doses at or below 0.2%, as was widely known in the field and shown on the package inserts for the products. (*See, e.g.*, EX-1008,

EX2227 (Gil Decl.) at ¶ 24;
see also EX1008 at 3; EX1068 at 4; EX1067 at 9, 14

245 IPR: Paper 25 at 19-20
600 IPR: Paper 21 at 20-21

Brimonidine Was Known to Cause Unwanted Side Effects, Including Eye Redness



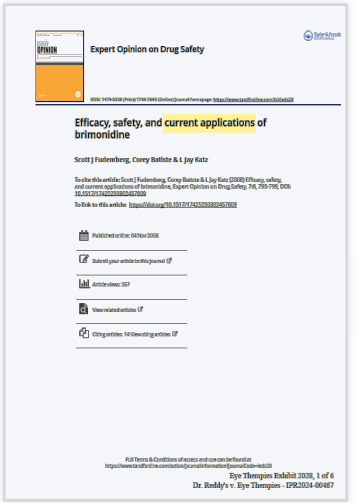
(12) STANDARD PATENT (11) Application No. AU 2002254265 B2
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Imidazole derivatives and their use as agonists selective at alpha 2B or 2B/2C adrenergic receptors

(51) International Patent Classification(s)
C07D 233/58 (2006.01) A61P 25/18 (2006.01)
A61K 31/4164 (2006.01) A61P 25/22 (2006.01)
A61K 31/4178 (2006.01) A61P 25/24 (2006.01)
A61K 31/421 (2006.01) A61P 25/28 (2006.01)
A61K 31/430 (2006.01) A61P 27/02 (2006.01)
A61K 31/4709 (2006.01) A61P 27/06 (2006.01)
A61K 31/4725 (2006.01) A61P 27/16 (2006.01)
A61K 31/4965 (2006.01) C07D 233/54 (2006.01)
A61K 31/538 (2006.01) C07D 233/64 (2006.01)
A61P 1/12 (2006.01) C07D 233/84 (2006.01)
A61P 7/12 (2006.01) C07D 233/94 (2006.01)
A61P 9/00 (2006.01) C07D 263/38 (2006.01)
A61P 9/04 (2006.01) C07D 401/06 (2006.01)
A61P 9/10 (2006.01) C07D 403/06 (2006.01)
A61P 9/12 (2006.01) C07D 405/06 (2006.01)
A61P 25/02 (2006.01) C07D 409/06 (2006.01)
A61P 25/04 (2006.01) C07D 413/12 (2006.01)
A61P 25/14 (2006.01) C07D 495/04 (2006.01)

(21) Application No: 2002254265 (22) Date of Filing: 2002.03.15
(87) WIPO No: WO02/076950
(30) Priority Data
(31) Number 09/815,362 (32) Date 2001.03.21 (33) Country US
(43) Publication Date: 2002.10.08
(43) Publication Journal Date: 2003.03.27
(44) Accepted Journal Date: 2008.05.15
(62) Divisional of: 744786 773668
(71) Applicant(s) Allergan, Inc.
(72) Inventor(s) Garst, Michael E.;Gil, Daniel W.;Burke, James A.;Harcourt, Dale A.;Munk, Stephen A.;Heidelbaugh, Todd M.;Chow, Ken;Wheeler, Larry A.;Gomez, Darlo G.
(74) Agent / Attorney Davies Collison Cave, 255 Elizabeth Street, Sydney, NSW, 2000
(56) Related Art
US 5621113
WO 9733577
WO 9738986
WO 9407866
WO 9100088

Eye Therapies Exhibit 2118, 1 of 130
Dr. Reddy's v. Eye Therapies - IPR2024-00467



Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-7645 (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Efficacy, safety, and current applications of brimonidine

Scott J Fudemberg, Corey Batiste & L Jay Katz

To cite this article: Scott J Fudemberg, Corey Batiste & L Jay Katz (2008) Efficacy, safety, and current applications of brimonidine, Expert Opinion on Drug Safety, 7:6, 795-799, DOI: 10.1517/14740330802457609

To link to this article: https://doi.org/10.1517/14740330802457609

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Eye Therapies Exhibit 2028, 1 of 6
Dr. Reddy's v. Eye Therapies - IPR2024-00467

(10) International Publication Number
WO 02/076950 A3

(54) Title: IMIDIAZOLE DERIVATIVES AND THEIR USE AS AGONISTS SELECTIVE AT ALPHA 2B OR 2B/2C ADRENERGIC RECEPTORS

(30) Priority Data:
09/815,362 21 March 2001 (21.03.2001) US

(71) Applicant: **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).

(72) Inventors: **CHOW, Ken**; 20 Tidal Surf, Newport Coast, CA 92657 (US). **GIL, Daniel, W.**; 2541 Point Del Mar, Corona Del Mar, CA 92625 (US). **BURKE, James, A.**; 2409 East Avalon, Santa Ana, CA 92705 (US). **HARCOURT, Dale, A.**; 2 Flagstone, Apt. #344, Irvine, CA 92606 (US). **GARST, Michael, E.**; 2627 Raqueta, Newport Beach, CA 92660 (US). **WHEELER, Larry, A.**; 18 Valley View, Irvine, CA 92715 (US). **MUNK,**

The prior art alpha2 adrenergic agonists, which activate all three alpha2 receptors, cause sedation, hypotension and bradycardia, preventing or severely limiting their use for treating diseases and disorders that are known to be ameliorated by them. Such diseases and disorders include

EX2118 (AU '265 Application) at 115:10-13

4. Safety evaluation

Chronic use of brimonidine is limited by the potential for allergy and intolerance. In the Brimonidine Study Group

trials, about 9% of patients experienced allergic reactions such as blepharitis, blepharoconjunctivitis or conjunctivitis, whereas 7.8% experienced conjunctival follicles and > 26% experienced some hyperemia [18]. Seventeen percent of patients

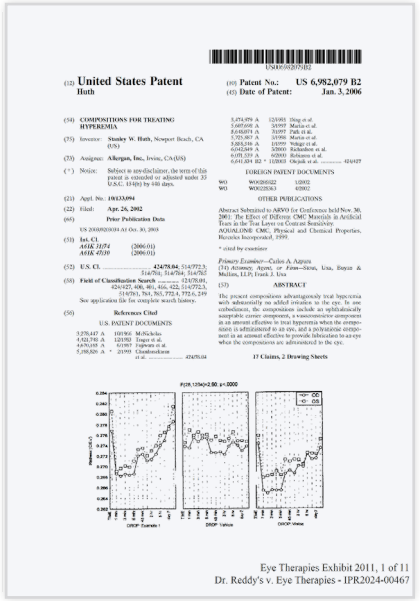
EX2028 (Fudemberg 2008) at 4;
EX2223 (Noecker Decl.) at ¶ 112

245 IPR: Paper 25 at 19-20
600 IPR: Paper 21 at 20-21

What Allergan Actually Did When It Wanted To Create A Redness Reliver



Dr. Daniel W. Gil
(Patentee's expert)



Eye Therapies Exhibit 2011, 1 of 11
Dr. Reddy's v. Eye Therapies - IPR2024-00467

at low concentrations like 0.025%, would work as a redness reducer. Rather, consistent with the knowledge in the art regarding brimonidine and its lower propensity for activating α1 receptors and causing vasoconstriction, Allergan scientists attempting to develop improved treatments for ocular hyperemia were focused on the use of α1-adrenergic agonists. (*E.g.*, EX-2011 (U.S. Patent No.

EX2227 (Gil Decl.) at ¶ 41

(12) **United States Patent**
Huth

(10) **Patent No.: US 6,982,079 B2**
(45) **Date of Patent: Jan. 3, 2006**

(54) **COMPOSITIONS FOR TREATING HYPEREMIA**

(75) Inventor: **Stanley W. Huth**, Newport Beach, CA (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 446 days.

(21) Appl. No.: **10/133,094**

(22) Filed: **Apr. 26, 2002**

In a very useful embodiment, the vasoconstrictor component comprises at least one alpha-1-adrenergic agonist. For example, the vasoconstrictor component may be selected from the group consisting of tetrahydrozoline, ephedrine, naphazoline, phenylephrine, salts thereof and mixtures thereof. More preferably, the vasoconstrictor component is selected from tetrahydrozoline, salts thereof and mixtures thereof. In one useful embodiment, the present composition

EX2011 at 2:27-35

245 IPR: Paper 25 at 2, 3, 19-20, 59, Paper 72 at 21.
600 IPR: Paper 21 at 2, 3, 21, 55, Paper 68 at 13.

Allergan and Dr. Gil *Never* Considered Using Brimonidine for Redness Reduction



Dr. Daniel W. Gil
(Patentee's expert)

41. To be clear, in my experience overseeing dozens of scientists working in ophthalmology at Allergan starting in 1988 and well past the 2008 priority date of the claimed invention, I do not recall anyone thinking that brimonidine, let alone at low concentrations like 0.025%, would work as a redness reducer. Rather, consistent with the knowledge in the art regarding brimonidine and its lower propensity for activating α1 receptors and causing vasoconstriction, Allergan scientists attempting to develop improved treatments for ocular hyperemia were focused on the use of α1-adrenergic agonists. (*E.g.*, EX-2011 (U.S. Patent No.

EX2227 (Gil Decl.) at ¶ 41

245 IPR: Paper 25 at 2, 3, 19-20, Paper 72 at 21.
600 IPR: Paper 21 at 2, 3, 21, Paper 68 at 13.

Allergan and Dr. Gil *Never* Considered Using Brimonidine for Redness Reduction



Dr. Daniel W. Gil
(Patentee's expert)

> 42. To the best of my knowledge, Allergan never applied for a patent or conducted any preclinical or clinical studies directed to the use of brimonidine—let alone at 0.025%—for reducing eye redness. The approval of LUMIFY, based on the discovery of the '245 patent family, surprised me and our group—at the time, the thinking was that it should have only reduced redness (and vasoconstricted) at high doses, not low. (EX-2003, Derick 1995 at 1; EX-1023, Robin 1998 at 2.)

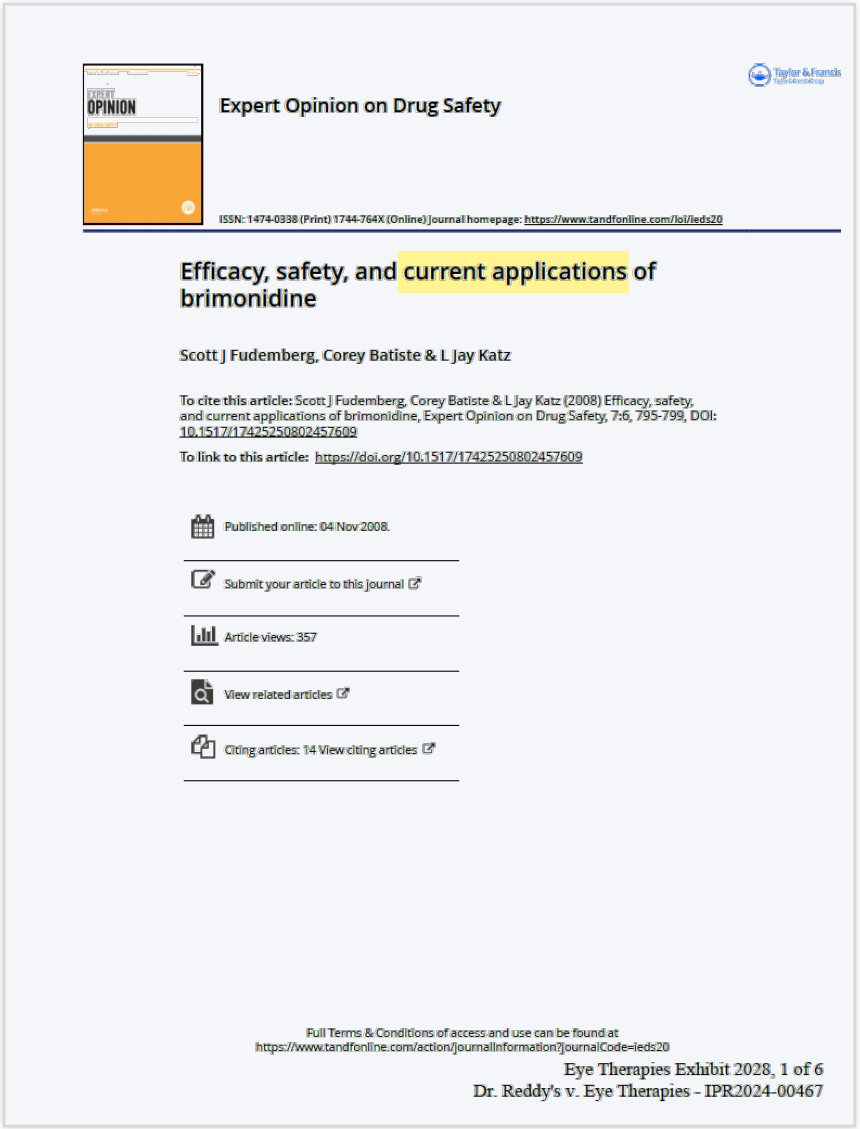
EX2227 (Gil Decl.) at ¶ 42

> *could that work?"* coupled with, *"wow, I wish we would have thought of that!"* What surprised me so much about the approval of LUMIFY—both upon approval and today—is the fact that 0.025% brimonidine, including a single drop of 0.025% brimonidine, actually ***reduces*** redness rather than ***causing*** it. This runs contrary to the basic pharmacology of the brimonidine molecule, which has been well-researched in the field of ophthalmology by top companies for decades. It is also

EX2227 (Gil Decl.) at ¶ 24

245 IPR: Paper 25 at 2, 3, 19-20, Paper 72 at 21.
600 IPR: Paper 21 at 2, 3, 21, Paper 68 at 13.

Contemporaneous Review Article of *Brimonidine's Current Applications*, Never Even Alludes to Its Use as a Redness Reliever



Expert Opinion on Drug Safety

ISSN: 1474-0338 (Print) 1744-764X (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Efficacy, safety, and current applications of brimonidine

Scott J Fudemberg, Corey Batiste & L Jay Katz

To cite this article: Scott J Fudemberg, Corey Batiste & L Jay Katz (2008) Efficacy, safety, and current applications of brimonidine, Expert Opinion on Drug Safety, 7:6, 795-799, DOI: 10.1517/17425250802457609

To link to this article: https://doi.org/10.1517/17425250802457609

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Eye Therapies Exhibit 2028, 1 of 6
Dr. Reddy's v. Eye Therapies - IPR2024-00467

application of this therapy. *Objective*: We review available evidence regarding the efficacy and side effect profile of brimonidine as well as its role in glaucoma management. *Results/conclusion*: Brimonidine is an important

glaucoma management. *Results/conclusion*: Brimonidine is an important component of topical glaucoma treatment that is most limited by local ocular intolerance.

4. Safety evaluation

Chronic use of brimonidine is limited by the potential for allergy and intolerance. In the Brimonidine Study Group

trials, about 9% of patients experienced allergic reactions such as blepharitis, blepharoconjunctivitis or conjunctivitis, whereas 7.8% experienced conjunctival follicles and > 26% experienced some hyperemia [18]. Seventeen percent of patients

Endnotes

12. Derick RJ, Robin AL, Walters TR, et al. Brimonidine tartrate: a one-month dose response study. Ophthalmology 1997;104(1):131-6. Published erratum appears in: Ophthalmology 1997;104(3):346

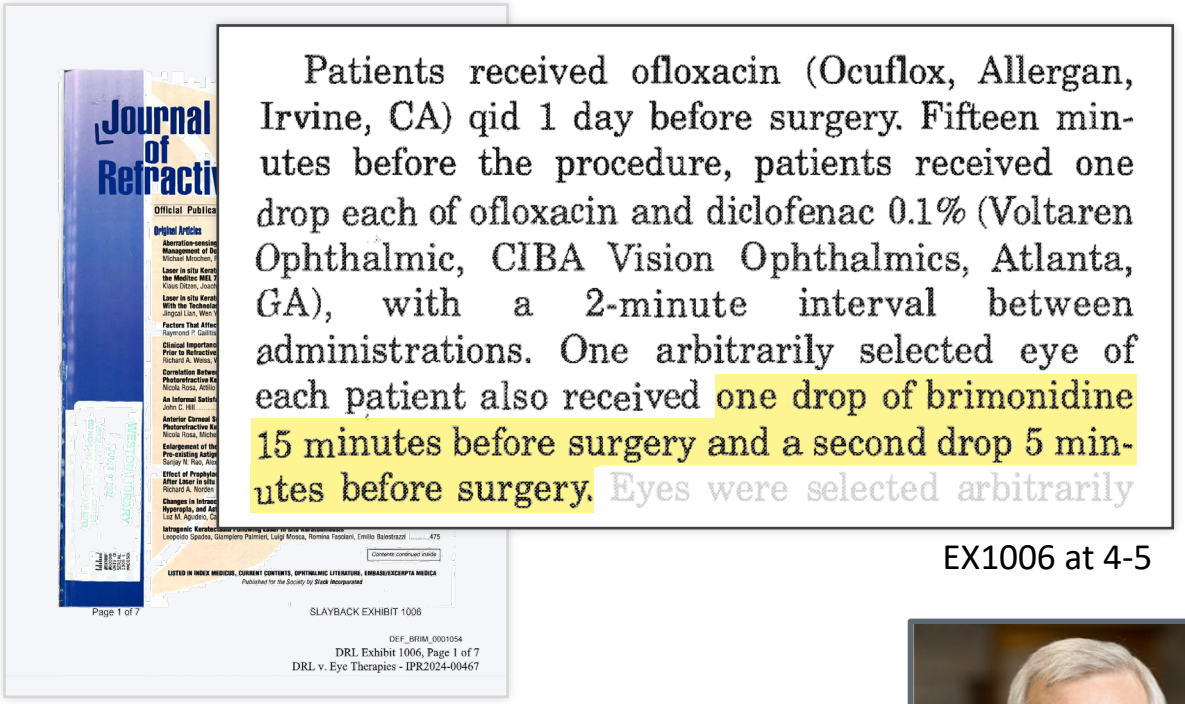
EX2028 (Fudemberg 2008) at 2, 4
245 IPR: EX2023 (Noecker Decl.) at ¶¶ 111-112, 122;
600 IPR: EX2023 (Noecker Decl.) at ¶¶ 115-116, 130

245 IPR: Paper 25 at 19-20, 29; Paper 72 at 23-24
600 IPR: Paper 21 at 3, 21-22, Paper 68 at 15-16.

Steady and Consistent Prior Art Messaging: Go *HIGH* to Reduce Redness

Steady and Consistent Prior Art Messaging: Go *HIGH* to Reduce Redness

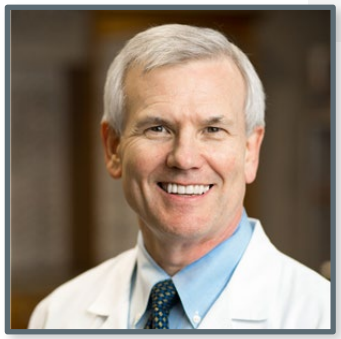
Norden (EX1006)



Patients received ofloxacin (Ocuflox, Allergan, Irvine, CA) qid 1 day before surgery. Fifteen minutes before the procedure, patients received one drop each of ofloxacin and diclofenac 0.1% (Voltaren Ophthalmic, CIBA Vision Ophthalmics, Atlanta, GA), with a 2-minute interval between administrations. One arbitrarily selected eye of each patient also received one drop of brimonidine 15 minutes before surgery and a second drop 5 minutes before surgery. Eyes were selected arbitrarily

EX1006 at 4-5

- ***Two*** drops x ***0.2%*** brimonidine → ***0.4%*** brimonidine
  - 16x higher than claim 1 of the '245 patent
  - Teaches no more than the Alphagan clinical trials
  - Dr. Galanis (Petitioners' expert) agreed Norden dosed high:



John Galanis, MD, FASC
(Petitioners' Expert)

Q. Okay. And you rely on Dr. Donnenfeld's testimony that Norden administered a dose of 0.4 percent brimonidine because Norden administered two drops of 0.2 percent brimonidine within a 10-minute period. Right?

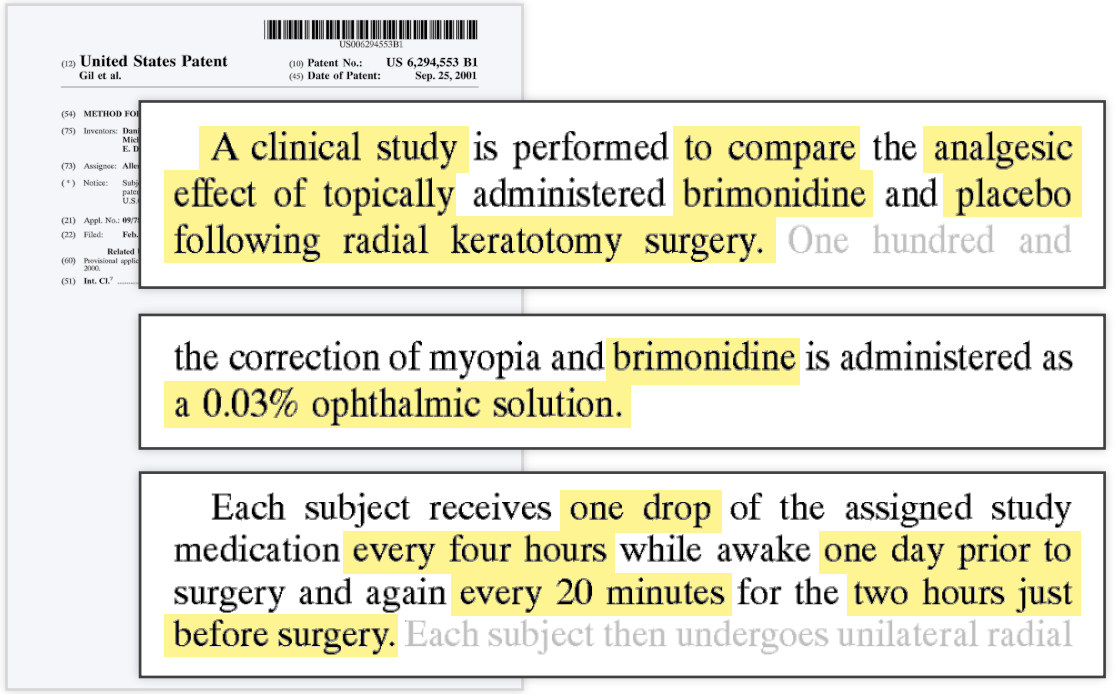
A. Correct.

EX2279 (Galanis Dep. Tr.) at 28:5-10.

245 IPR: Paper 25 at 41, Paper 72 at 20-21;
600 IPR: Paper 21 at 35, Paper 68 at 12-13.

Gil (EX1004) Teaches Brimonidine Dosing Regimens Far Exceeding a Single Drop of 0.025% Brimonidine

Gil Example 1 – prophetic and "data-free"



(12) **United States Patent**
Gil et al.

(10) Patent No.: US 6,294,553 B1
(45) Date of Patent: Sep. 25, 2001

A clinical study is performed to compare the analgesic effect of topically administered brimonidine and placebo following radial keratotomy surgery. One hundred and

the correction of myopia and brimonidine is administered as a 0.03% ophthalmic solution.

Each subject receives one drop of the assigned study medication every four hours while awake one day prior to surgery and again every 20 minutes for the two hours just before surgery. Each subject then undergoes unilateral radial

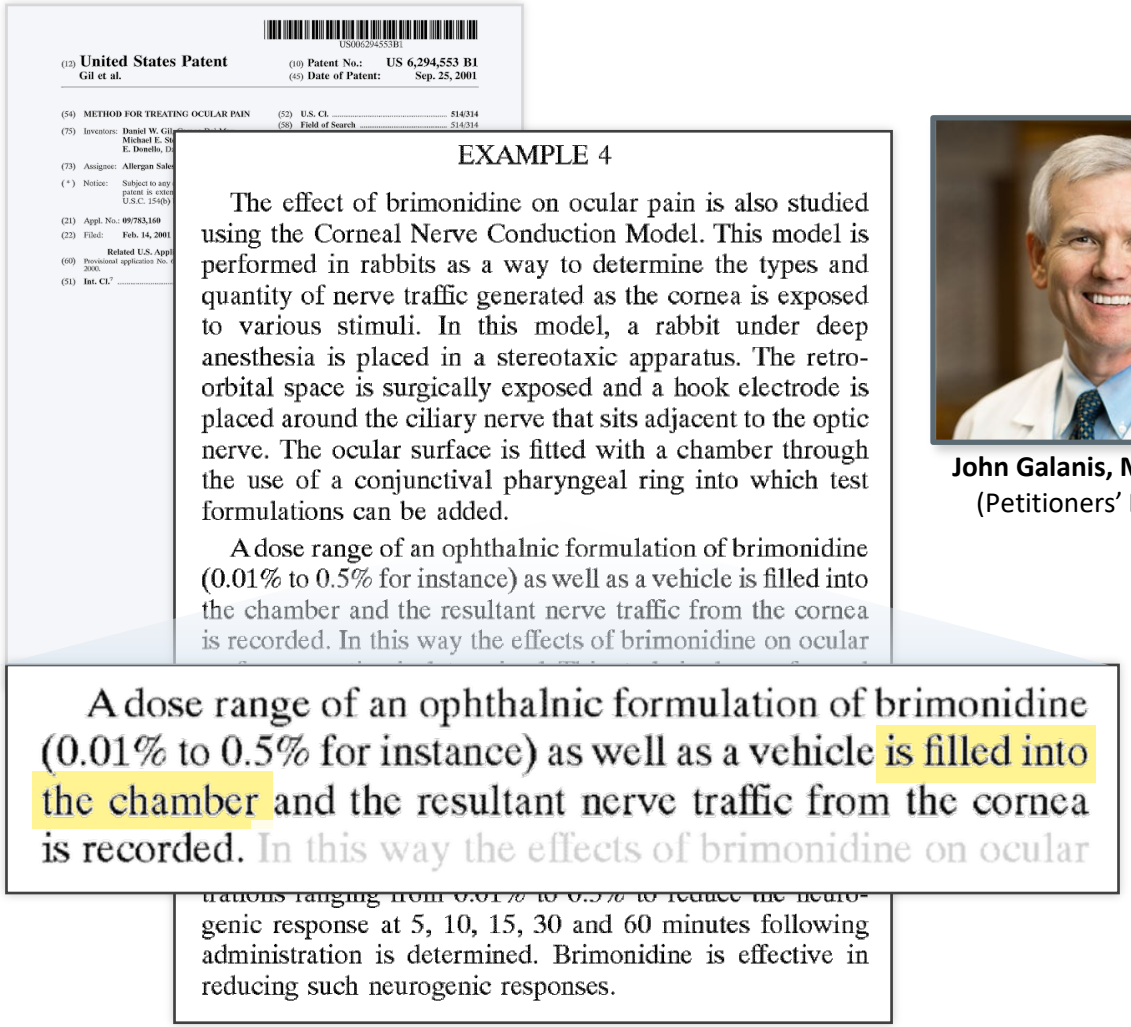
keratotomy. Following surgery, each subject receives one drop of the study medication in the operated eye every four hours while awake for 14 consecutive days. Postoperative examinations occur at days 1, 3, 7 and 14.

EX1004 (Gil) at 4:45-5:2

- Loading dose regimen of ***multiple drops of 0.03%*** brimonidine to relieve pain from ocular surgery
- Just prior to surgery, 6 to 7 drops of 0.03% → ***0.2%*** brimonidine
  - no better than Alphagan clinical trials, which at least taught 0.2% whitens conjunctiva
- ***8x*** higher than a single drop of 0.025% brimonidine

245 IPR: Paper 25 at 24-28, Paper 72 at 19-21;
600 IPR: Paper 21 at 22-26, Paper 68 at 11-13.

Gil Example 4: Prophetic and "Data-Free" Pain Model Study Led POSAs to High Doses of Brimonidine



US006294553B1

(12) **United States Patent**
Gil et al.

(10) Patent No.: US 6,294,553 B1
(45) Date of Patent: Sep. 25, 2001

(54) METHOD FOR TREATING OCULAR PAIN

(52) U.S. Cl. 514/314
(58) Field of Search 514/314

(75) Inventors: Daniel W. Gil[illegible]
Michael E. St[illegible]
E. Donello, D[illegible]

(73) Assignee: Allergan Sales

(*) Notice: Subject to any [illegible] patent is exten[illegible] U.S.C. 154(b)

(21) Appl. No.: 09/783,160

(22) Filed: Feb. 14, 2001

Related U.S. Appl[illegible]

(60) Provisional application No. [illegible] 2000.

(51) Int. Cl.[illegible]

EXAMPLE 4

The effect of brimonidine on ocular pain is also studied using the Corneal Nerve Conduction Model. This model is performed in rabbits as a way to determine the types and quantity of nerve traffic generated as the cornea is exposed to various stimuli. In this model, a rabbit under deep anesthesia is placed in a stereotaxic apparatus. The retro-orbital space is surgically exposed and a hook electrode is placed around the ciliary nerve that sits adjacent to the optic nerve. The ocular surface is fitted with a chamber through the use of a conjunctival pharyngeal ring into which test formulations can be added.

A dose range of an ophthalnic formulation of brimonidine (0.01% to 0.5% for instance) as well as a vehicle is filled into the chamber and the resultant nerve traffic from the cornea is recorded. In this way the effects of brimonidine on ocular

A dose range of an ophthalnic formulation of brimonidine (0.01% to 0.5% for instance) as well as a vehicle is filled into the chamber and the resultant nerve traffic from the cornea is recorded. In this way the effects of brimonidine on ocular

[illegible] ranging from 0.01% to 0.5% to reduce the neurogenic response at 5, 10, 15, 30 and 60 minutes following administration is determined. Brimonidine is effective in reducing such neurogenic responses.

EX1004 (Gil) at 5:18-46

John Galanis, MD, FASC
(Petitioners' Expert)

- Dr. Galanis admitted rabbit model incapable of measuring redness or its reduction

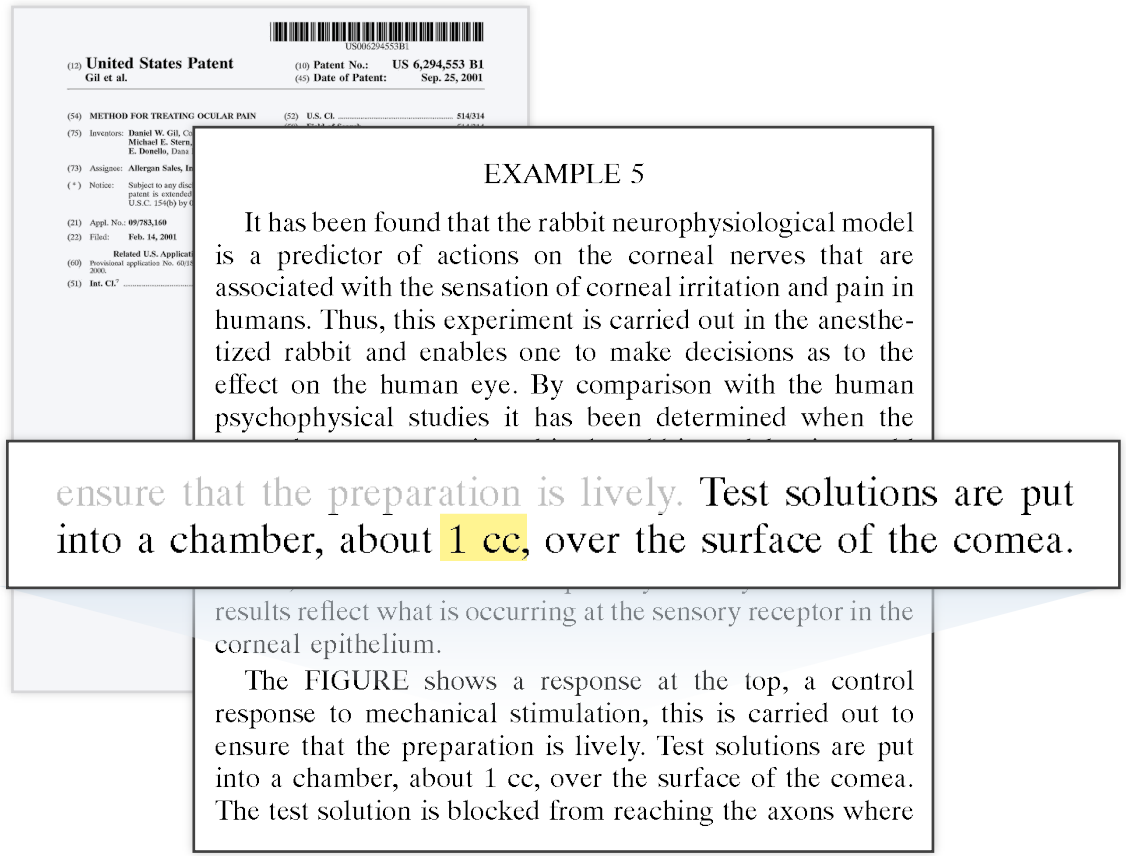
> Q. But you agree that the model itself is not capable of actually making an assessment of whether redness exists or whether it was reduced, correct?
>
> **A. It measures pain, that's correct then.**

EX-2017, 136:21-137:1

- Chamber on rabbit's eye filled with ***1 cc*** of brimonidine solution (*see* EX1004 at 5:65-66)
  - Alphagan NDA states standard/average brimonidine eyedrop = 35 µL (EX1030 at 20)
  - Dr. Galanis agreed 1cc of brimonidine at 35 µL = ***28-29 drops*** (EX2279, 39:14-40:3)
- Assuming 20-30 drops in 1 cc, 0.01% would be 0.2% to 0.3% dose of brimonidine

245 IPR: Paper 25 at 26-28 and 31-33, Paper 72 at 19-21;
600 IPR: Paper 21 at 18 and 24-26, Paper 68 at 11-13.

Gil Example 5 Ocularly Applied 1 cc of 0.2% Brimonidine



(12) **United States Patent**
Gil et al.

(10) Patent No.: US 6,294,553 B1
(45) Date of Patent: Sep. 25, 2001

(54) METHOD FOR TREATING OCULAR PAIN

EXAMPLE 5

It has been found that the rabbit neurophysiological model is a predictor of actions on the corneal nerves that are associated with the sensation of corneal irritation and pain in humans. Thus, this experiment is carried out in the anesthetized rabbit and enables one to make decisions as to the effect on the human eye. By comparison with the human psychophysical studies it has been determined when the

ensure that the preparation is lively. Test solutions are put into a chamber, about 1 cc, over the surface of the comea.

results reflect what is occurring at the sensory receptor in the corneal epithelium.

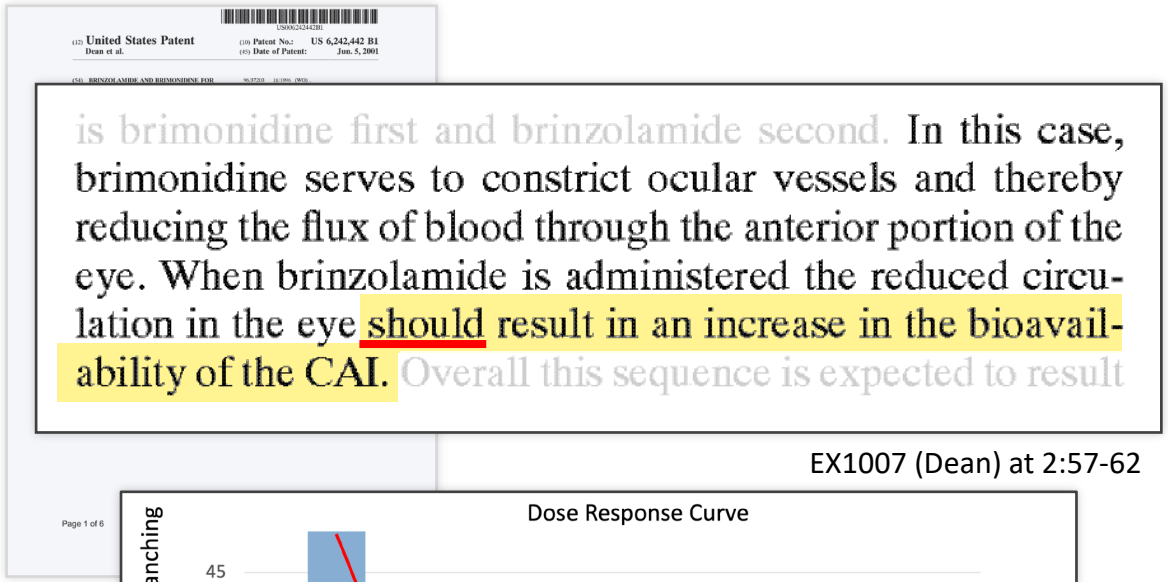
The FIGURE shows a response at the top, a control response to mechanical stimulation, this is carried out to ensure that the preparation is lively. Test solutions are put into a chamber, about 1 cc, over the surface of the comea. The test solution is blocked from reaching the axons where

EX1004 (Gil) at 5:65-66

- ***1 cc*** of brimonidine would be the equivalent of delivering 20-30 drops of 0.2% brimonidine
- Far exceeds what a single drop of 0.025% brimonidine would ocularly deliver
- Example 5 (and Example 4) evaluated pain relief, not redness reduction
- No better than the Alphagan clinical studies, which at least measured ***AND*** statistically analyzed brimonidine's conjunctival whitening/blanching effect

245 IPR: Paper 25 at 32-33, Paper 72 at 6 and 19-20;
600 IPR: Paper 21 at 26, Paper 68 at 11-12.

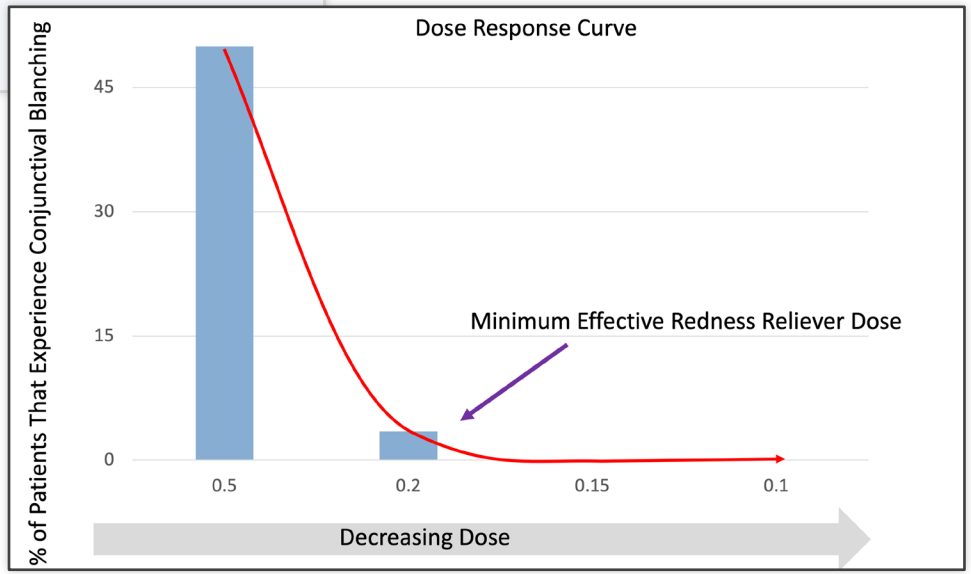
Dean, Read in View of the Alphagan Clinical Trials, Would Not Have Led POSAs to Lower Brimonidine's Dose Below 0.2% to Reduce Redness



(12) United States Patent
Dean et al.
(10) Patent No.: US 6,242,442 B1
(45) Date of Patent: Jun. 5, 2001

is brimonidine first and brinzolamide second. In this case, brimonidine serves to constrict ocular vessels and thereby reducing the flux of blood through the anterior portion of the eye. When brinzolamide is administered the reduced circulation in the eye should result in an increase in the bioavailability of the CAI. Overall this sequence is expected to result

EX1007 (Dean) at 2:57-62



- ***Zero-data*** hypothesis that all concentrations of brimonidine would vasoconstrict in the front of eye and increase brinzolamide's bioavailability
- Alphagan clinical studies established ~0.2% brimonidine as the minimum effective dose for redness reduction
  - POSAs - brimonidine *might* exert enough vasoconstriction to increase brinzolamide's absorption, but not enough to reduce redness at low doses (245 IPR: EX2223 (Noecker Decl.) at ¶¶ 152, 164; 600 IPR: EX2223 (Noecker Decl.) at ¶159)
- POSAs disincentivized to dose brimonidine below 0.2% because it would expectedly eliminate brimonidine's redness reduction effect

EX1067 (ALPHAGAN® Labels);
EX1068 (ALPHAGAN® P Label)

245 IPR: Paper 25 at 18 and 28-29, Paper 72 at 21-22;
600 IPR: Paper 21 at 19 and 30-31, Paper 68 at 14-15.

Discouraging Modifications that Cut Against the Goal

"The district court, applying [teaching away] standard, credited … testimony … that a skilled artisan 'would have been discouraged from incorporating the formulations in Controls 3 and 91' because ***'the data cut against the very goal a [skilled artisan] would have been trying to achieve***—a stable product with a consistent dose.'… The district court concluded, therefore, that 'Rogueda teaches away and does not render the claims obvious.' We discern no clear error in this finding and therefore affirm the district court's determination of nonobviousness."

AstraZeneca AB v. Mylan Pharms. Inc., 19 F.4th 1325, 1337 (Fed. Cir. 2021) (emphasis added)

245 IPR: Paper 25 at 38-48, Paper 72 at 24-25;
600 IPR: Paper 21 at 34-43, Paper 68 at 16-17.

No Presumption of Obviousness

Not Presumptively Obvious That One Drop of 0.025% Brimonidine Would Reduce Eye Redness

Together, Gil and Dean cover every known concentration of brimonidine

- Covering everything effectively tells POSAs nothing



"It may also be true here that 'the disclosed range[s are] so broad as to encompass a very large number of possible distinct compositions,' … such that they do not teach any specific amounts or combinations and that the burden of producing evidence of teaching away, unexpected results, and other pertinent secondary considerations did not shift to Allergan."

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1305 (Fed. Cir. 2015)

245 IPR: Paper 25 at 40, Paper 72 at 24-25; Paper 6 at 3
600 IPR: Paper 21 at 34, Paper 68 at 16-17; Paper 6 at 4.

Teaching Away and Unexpected Results Dissolves the Overlapping Ranges Presumption

Requiring consideration of all evidence *anew*



"When rebuttal evidence is provided, the *prima facie* case ***dissolves***, and the decision is made on the entirety of the evidence."

In re Kumar, 418 F.3d 1361, 1366 (Fed. Cir. 2005) (emphasis added)

245 IPR: Paper 72 at 24; 600 IPR: Paper 68 at 16.

Objective Evidence of Nonobviousness Dissipates Overlapping Ranges Presumption

- **Unexpected results** – low dose brimonidine not expected to work
  - Unexpectedly and beneficially, one drop 0.025% brimonidine reduced redness ***6x greater*** than standard of care, Visine, without rebound or tachyphylaxis
  - The unexpected results are different in kind
    - *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306-07 (Fed. Cir. 2015) (claimed invention demonstrating a difference between an effective and safe drug versus one with significant side effects that led to patient noncompliance "is an unexpected difference in kind that supports non-obviousness.")
- **Industry praise and commercial success**
  - Superior efficacy and safety profile of claimed method (embodied in use of Lumify) led to industry praise and then to commercial success

245 IPR: Paper 25 at 54-61, Paper 72 at 25-27;
600 IPR: Paper 21 at 50-57, Paper 68 at 17-19.

Objective Indicia Confer Patentability

Legal Construct for Determining the Closest Prior Art for an Unexpected Results Comparison

- *In re Merchant,* 575 F.2d 865 (CCPA 1978) provides the legal construct for selecting closest prior art
  - Merchant's claimed invention: method of removing HF from gaseous HCl using dry technique (significant claim element)
  - The CCPA selected as closest prior art process that aligned with claimed invention's purpose – method of removing HF from gaseous HCl
  - Rejected the Board's choice of method of removing HF from air using a dry technique
    - The CCPA court did not choose the process with the dry technique
    - Stated chasing every prior art method that used a significant element would make every reference "closest"
    - Chose method that had the greatest alignment with the claimed invention, i.e., one that achieved the same end result as the claimed invention

245 IPR: Paper 21 at 50; 600 IPR: Paper 25 at 45-46.

Starting Point for Determining the Closest Prior Art Begins with the Claimed Method of *Reducing Eye Redness*

- Bedrock principle of patent law is that ***the claim*** defines the scope of protection and exclusionary right
  - "[T]he name of the game is the claim." *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1298 (Fed. Cir. 2014)
- Here, the claimed invention is a method of ***reducing eye redness***
- Gil Example 1 disqualified as closest prior art
  - It is *not* a method of reducing eye redness but a method of reducing ocular pain
  - The Board already found that in the '724 IPR – "a POSA would not have read Gil's disclosure [in Example 1] of administering brimonidine with the express intent to treat eye pain as necessarily an intent to treat eye redness." EX1003 ('742 IPR FWD) at 35.

245 IPR: Paper 25 at 52; 600 IPR: Paper 21 at 48.

0.03% Brimonidine Cannot Legally Constitute the Closest Prior Art

- 0.03% brimonidine is what the prior Board in the ’742 IPR contended was obvious
  - “In contrast, here, Gil clearly teaches that 0.03% brimonidine is topically applied to patients’ eyes having an ocular condition, and suggests that it would be effective in reducing eye redness.” EX1003 (’742 IPR FWD) at 63-64 (emphasis added).
    - Note: Gil does not teach a single drop of 0.03% brimonidine, but a loading dose that approaches 0.2%
- *In Millennium v. Sandoz*, the CAFC held the closest prior art comparator for unexpected results must be “disclosed, prepared, or tested.” 862 F.3d 1356, 1368 (Fed. Cir. 2017).
  - Because “[u]nexpected results are shown in comparison to what was known, not what was unknown,” the patentee was not required to create a new, undisclosed product from the prior art and test that product against the invention. Id. (emphasis added).
- Requiring a patentee to compare its invention to what is alleged to be obvious would require comparing the invention against itself – that is not the law

245 IPR: Paper 25 at 50-51 and 53-54, Paper 72 at 25-26;
600 IPR: Paper 21 at 45-47 and 49-50, Paper 68 at 17-18.

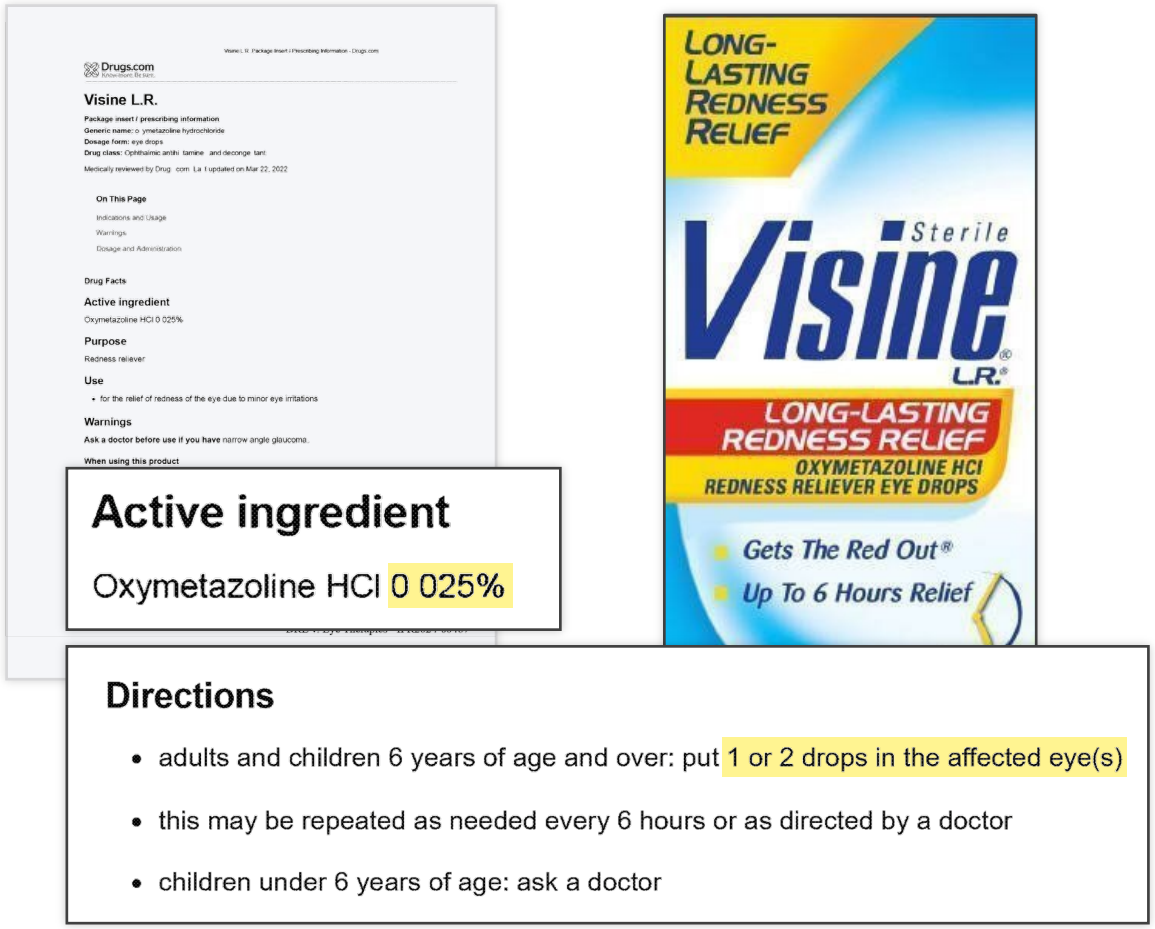
More Glaring Legal Problems with Comparing Lumify's Redness Reduction Ability Against 0.03% Brimonidine

Requires deconstructing Gil Example 1 and creating an embodiment Gil never disclosed

- Gil Example 1 administers not a single drop but 6-7 drops of 0.03% brimonidine, approaching what a single drop of 0.2% would ocularly deliver
  - EX1004 (Gil) at 4:45-5:2
- Brimonidine is not administered as the sole active but co-administered with other actives, some of which reduce redness
  - EX2018 (Sher '742 IPR Dep. Tr.) at 22:24-23:13; 245 IPR: EX2223 (Noecker Decl.) at ¶142; 600 IPR: EX2223 (Noecker Decl.) at ¶ 141
- Gil Example 1 is not a method of reducing redness, but a method of reducing ocular pain
  - EX1003 ('742 IPR FWD) at 33

245 IPR: Paper 25 at 24-25, 40-41 and 52-54, Paper 72 at 19-20;
600 IPR: Paper 21 at 24-26, 34-35, and 47-50, Paper 68 at 11-12.

Numerous Reasons Why Visine L.R. is the Legally Proper Closest Prior Art to the *Claimed Invention*



EX1143 (Visine L.R.) at 1, 2

- Visine L.R. has far more elements in common with the claimed invention than Gil Example 1.
  - Directed to reducing eye redness
  - Administers a single drop in a single step
  - Doses the same concentration (0.025%)
  - Achieves actual redness reduction

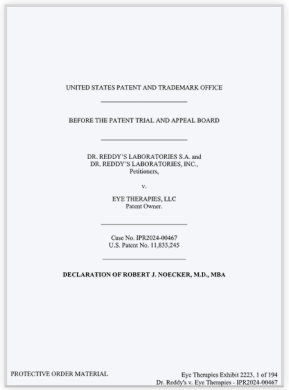
245 IPR: Paper 21 at 49-54, Paper 72 at 25-26;
600 IPR: Paper 25 at 44-50, Paper 68 at 17-18.

No Expectation in the Art That One Drop of 0.025% Brimonidine Would Reduce Eye Redness

- Pre-2008 statistically-analyzed, robust human clinical studies established brimonidine's minimum effective redness-reducing dose was about 0.2%


Preclinical Evaluation of Brimonidine

- Because of its low affinity for α_1-adrenoreceptors the art taught "**brimonidine** would be the **least likely to produce** α_1-adrenoceptor-mediated side effects, such as … **ocular vasoconstriction**"
  - EX1035 (Burke) at 2


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. REDDY'S LABORATORIES S.A. and DR. REDDY'S LABORATORIES, INC., Petitioners, v. EYE THERAPIES, LLC Patent Owner.

Case No. IPR2024-00467
U.S. Patent No. 11,833,245

DECLARATION OF ROBERT J. NOECKER, M.D., MBA

PROTECTIVE ORDER MATERIAL

- **Visine's oxymetazoline**, a mixed α_1/α_2 agonist, had a 200-fold greater affinity for α1 over α2 than brimonidine and would have been **expected to vastly outperformed Lumify**.
  - 245 IPR: EX2223 (Noecker Decl.) at ¶¶223-224; 600 IPR: EX2223 (Noecker Decl.) at ¶¶ 214-217

245 IPR: Paper 25 at 56; 600 IPR: Paper 21 at 52.

Lumify Not Only Worked, It Unexpectedly Reduced Redness Up to *6x Better* Than Standard of Care, Visine L.R.

1.0 TITLE PAGE

Study Title:	A Single-Center, Randomized, Double-Masked, Placebo and Active Controlled, Dose-Ranging Evaluation of the Duration of Action of Brimonidine Tartrate Ophthalmic Solution in the Prevention of Ocular Redness Induced by Conjunctival Allergen Challenge (CAC)
Study Drug:	Brimonidine tartrate
Population Studied:	Subjects with mild ongoing allergic conjunctivitis
Brief Description:	Randomized, double-masked, single-center study to evaluate the safety, efficacy, and dose response of brimonidine tartrate 0.01% and 0.025% ophthalmic solution as compared to placebo in the prevention of allergen-induced conjunctival redness using a conjunctival allergen challenge (CAC) model.
Study Sponsor:	Eye Therapies, LLC S&R Professional Building 26933 Camino De Estrella, 2nd Floor Dana Point, CA 92624
Study Number:	10-100-0008
Development Phase:	Phase 2
Study Initiated:	21 January 2011 (first subject, first visit)
Study Completed:	19 March 2011 (last subject completed)
Medical Monitor:	Joseph Ciolino, MD Telephone: (978) 685-8900
Sponsor Signatory	James W. McCollum
Date of Report:	March 1, 2012

Statement of Compliance with Good Clinical Practice

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP).

Confidentiality Statement

This Clinical Study Report is confidential and the information available within it may not be reproduced or otherwise disseminated.

PROTECTIVE ORDER MATERIAL

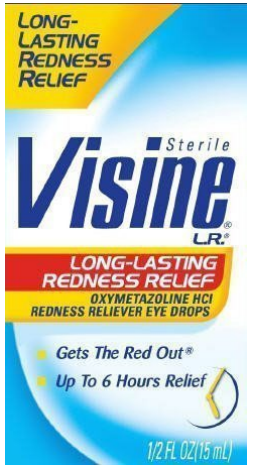
Eye Therapies Exhibit 2166, 1 of 29
Slayback v. Eye Therapies - IPR2022-00142

COUNSELS' EYES ONLY – SUBJECT TO DISCOVERY CONFIDENTIALITY ORDER BAU-LUM00069893

0.025% Brimonidine v. 0.025% Oxymetazoline Redness Reduction	
Conjunctiva	Episclera
Brimonidine about 3.3-5.5 times better than Visine L.R. (oxymetazoline)	**Brimonidine about 4.3-6.5 times better** than Visine L.R. (oxymetazoline)
Duration of action: *30% longer*	



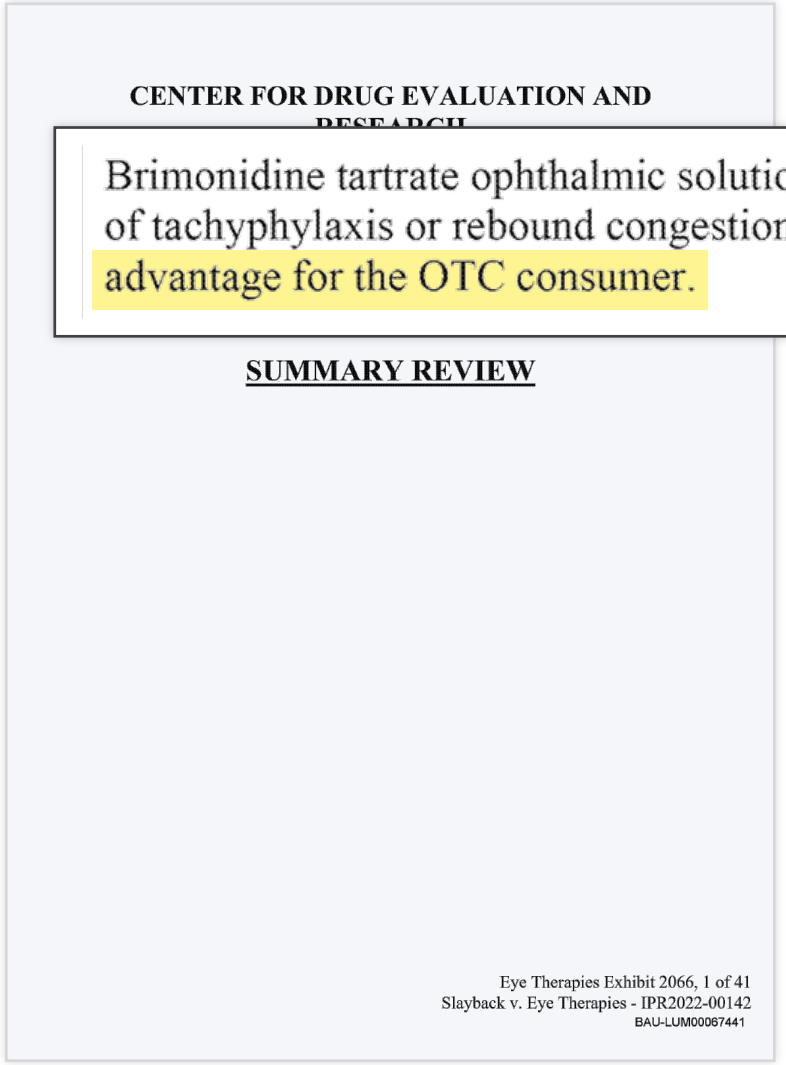
VS.



245 IPR: EX2223 (Noecker Decl.) at ¶¶223-228;
600 IPR: EX2223 (Noecker Decl.) at ¶¶214-223

245 IPR: Paper 25 at 10 and 54-57, Paper 72 at 24-25;
600 IPR: Paper 21 at 10-11 and 50-53, Paper 68 at 17.

Unexpectedly and Beneficially, Lumify Exhibited No Tachyphylaxis or Rebound Hyperemia



CENTER FOR DRUG EVALUATION AND RESEARCH

Brimonidine tartrate ophthalmic solution 0.025% did not show tachyphylaxis or rebound congestion in clinical trials. The absence of tachyphylaxis or rebound congestion with an OTC ophthalmic vasoconstrictor to relieve redness of the eye is a potential advantage for the OTC consumer.

SUMMARY REVIEW

Eye Therapies Exhibit 2066, 1 of 41
Slayback v. Eye Therapies - IPR2022-00142
BAU-LUM00067441

EX-2027 (Lumify NDA Summary Review) at 3

- FDA independently recognized that Lumify surprisingly did not show tachyphylaxis or rebound hyperemia in clinical trials
- A distinctly meaningful "real-world" advantage over the commercial products and important for OTC products susceptible to noncompliant misuse. 245 IPR: EX2223 (Noecker Decl.) at ¶¶235-236; 600 IPR: EX2223 (Noecker Decl.) at ¶¶229-230.
- Unexpectedly superior efficacy and safety profile of claimed method (embodied in use of Lumify) represents ***a difference in kind***, providing substantial objective evidence of non-obviousness

245 IPR: Paper 25 at 10 and 57, Paper 72 at 24-35;
600 IPR: Paper 21 at 11 and 53, Paper 68 at 17.

Lumify's Heretofore Unrealizable Efficacy and Safety Profile was a Difference in Kind and Foundational to Its Industry Praise and Commercial Success

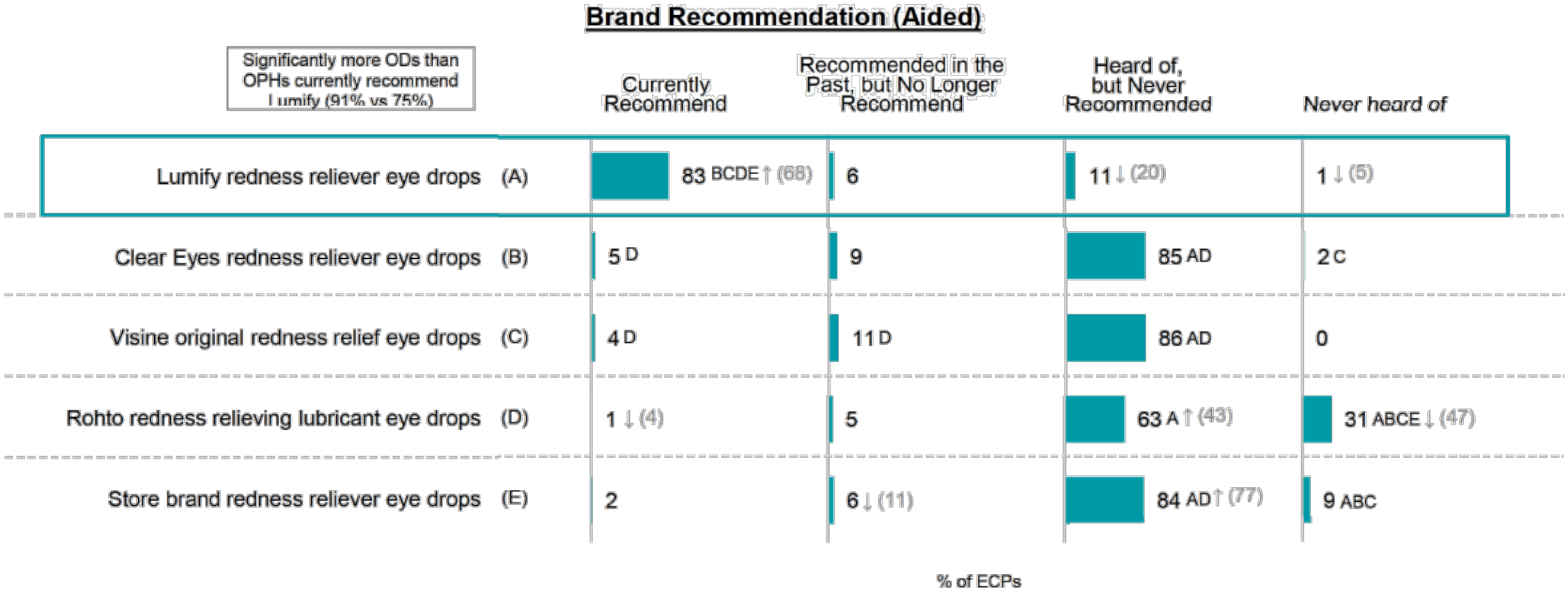
"The claimed formulation, which comprises 0.01% bimatoprost and 200 ppm BAK, unexpectedly maintained the IOP-lowering efficacy of Lumigan 0.03%, while exhibiting reduced incidence and severity of hyperemia, even though the prior art taught that BAK could cause hyperemia at high concentrations. Those results exhibited by the claimed formulation thus constitute an unexpected difference in kind, viz., the difference between an effective and safe drug and one with significant side effects that caused many patients to discontinue treatment."

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1306-1307 (Fed. Cir. 2015)

245 IPR: Paper 25 at 57, Paper 72 at 24-25;
600 IPR: Paper 21 at 53, Paper 68 at 17.

Lumify Has Generated Significant Industry Praise

Lumify is the most often currently recommended redness reliever eye drop with four in five ECPs currently recommending. Current recommendations for Lumify are led largely by Optometrists.



Base: Total ECPs (n=200)
Uppercase letters denote a significant difference at the 90% confidence level
↑↓ denote significant differences at the 90% confidence level vs. previous wave
A2. Please indicate your familiarity with each of the following brands of over-the-counter (OTC) redness reliever eye drops.

BAUSCH+LOMB

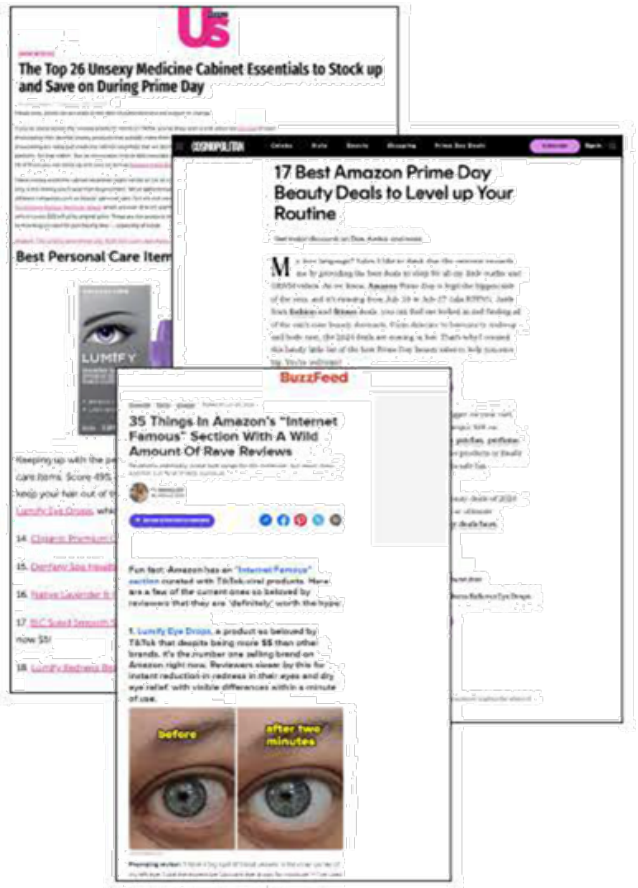
13

EX-2070 at 13

245 IPR: Paper 25 at 60-61, Paper 72 at 26-27;
600 IPR: Paper 21 at 56-57, Paper 68 at 18-19.

Lumify Has Generated Significant Industry Praise

PRIME DAY COVERAGE



NATIONAL TV



"Tips to revamp your skin and eye care routine for the summer." Dr.Tsai joined GMA to share her tips for protecting eyes during the summer heat.

WALL STREET JOURNAL



LUMIFY is mentioned in the Wall Street Journal in a piece titled, "You Look Tired. We Can Help. A Men's Guide to Looking More Alert at Work."

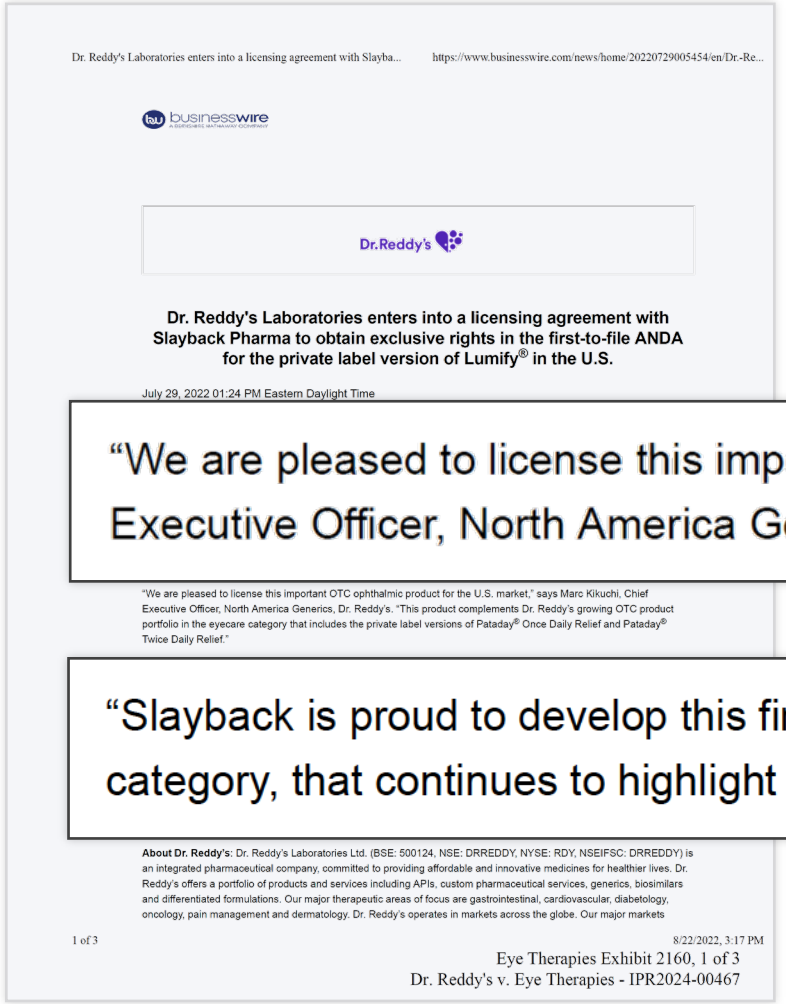
CELEBRITIES



EX-2063 at 3

245 IPR: Paper 25 at 60-61, Paper 72 at 26-27;
600 IPR: Paper 21 at 56-57; Paper 68 at 18-19.

Lumify's Industry Praise Extends to Petitioners and Their Licensor



Dr. Reddy's Laboratories enters into a licensing agreement with Slayba... https://www.businesswire.com/news/home/20220729005454/en/Dr.-Re...

businesswire

Dr.Reddy's

Dr. Reddy's Laboratories enters into a licensing agreement with Slayback Pharma to obtain exclusive rights in the first-to-file ANDA for the private label version of Lumify® in the U.S.

July 29, 2022 01:24 PM Eastern Daylight Time

"We are pleased to license this important OTC ophthalmic product for the U.S. market," says Marc Kikuchi, Chief Executive Officer, North America Generics, Dr. Reddy's. "This product complements Dr. Reddy's growing OTC product portfolio in the eyecare category that includes the private label versions of Pataday® Once Daily Relief and Pataday® Twice Daily Relief."

About Dr. Reddy's: Dr. Reddy's Laboratories Ltd. (BSE: 500124, NSE: DRREDDY, NYSE: RDY, NSEIFSC: DRREDDY) is an integrated pharmaceutical company, committed to providing affordable and innovative medicines for healthier lives. Dr. Reddy's offers a portfolio of products and services including APIs, custom pharmaceutical services, generics, biosimilars and differentiated formulations. Our major therapeutic areas of focus are gastrointestinal, cardiovascular, diabetology, oncology, pain management and dermatology. Dr. Reddy's operates in markets across the globe. Our major markets

1 of 3 8/22/2022, 3:17 PM

Eye Therapies Exhibit 2160, 1 of 3
Dr. Reddy's v. Eye Therapies - IPR2024-00467

Dr. Reddy's Laboratories enters into a licensing agreement with Slayback Pharma to obtain exclusive rights in the first-to-file ANDA for the private label version of Lumify® in the U.S.

July 29, 2022 01:24 PM Eastern Daylight Time

"We are pleased to license this important OTC ophthalmic product for the U.S. market," says Marc Kikuchi, Chief Executive Officer, North America Generics, Dr. Reddy's. "This product complements Dr. Reddy's growing OTC product

"Slayback is proud to develop this first-to-file ANDA for Lumify®, a significant OTC product in the eye redness reliever category, that continues to highlight the R&D capability of the company," said Ajay Singh, CEO and Founder of Slayback.

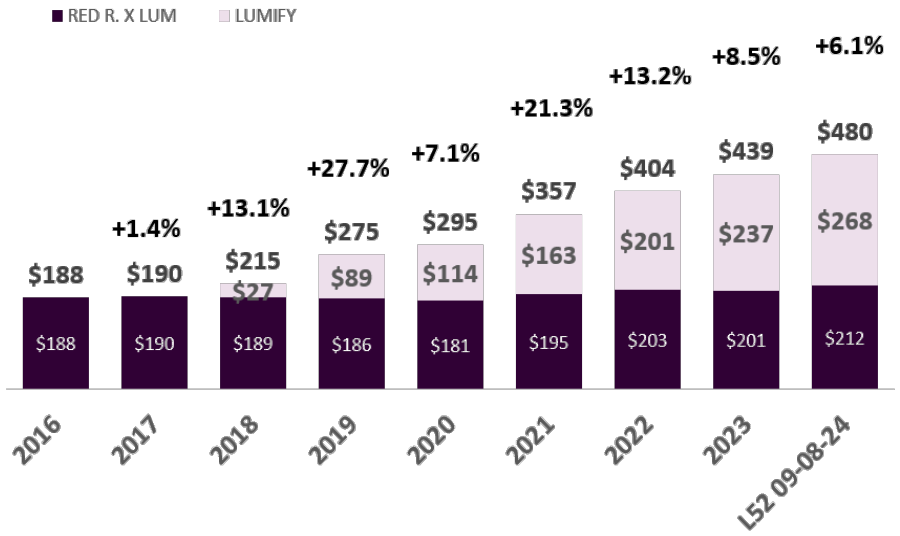
EX-2160 at 1

245 IPR: Paper 25 at 60-61, Paper 72 at 26-27;
600 IPR: Paper 21 at 56-57, Paper 68 at 18-19.

Lumify's Substantial Commercial Success Is Objective Evidence of Non-Obviousness

"A prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent. Once the patentee demonstrates a prima facie nexus, ***the burden of coming forward with evidence in rebuttal shifts to the challenger***."

Crocs, Inc. v. Int'l Trade Comm'n, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010) (emphasis added) (internal citation omitted)



- Overall redness reliever marketplace has grown by **152%** since 2017, the year before Lumify's launch
- All redness relievers combined other than Lumify only grew **11.5%** during the same time period
- Lumify has driven the entire category

245 IPR: Paper 25 at 58-59 and 61-63, Paper 72 at 26-27;
600 IPR: Paper 21 at 54-55 and 57-59, Paper 68 at 18-19;
EX-2230 (Ferris Decl.) at ¶26; EX-2075 at 3.

Petitioners Cannot Rebut Lumify's Presumed Nexus With the Challenged Patent Claims

- Petitioners' chief arguments for lack of nexus are that the patented features are found in the prior art (incorrect, *see supra*) and that Lumify's success is due to marketing, not the patented features
- But advertising expenses as a share of gross net revenue for Lumify have steadily and dramatically ***fallen*** since the months following launch in 2018, while sales have steadily increased
- Petitioners' expert admitted this evidence was ***not*** before the Board in the '142 IPR

> Q. There was no appendix equivalent to this one in the '742 declaration by Mr. Jarosz; you would agree?
>
> **A. That was not in the '742 declaration that I recall.**

EX-2281 (Masztak Dep. Tr.) at 184:8-12

245 IPR: Paper 25 at 61-63, Paper 72 at 26-27;
600 IPR: Paper 25 at 57-59, Paper 68 at 18-19;
EX-2229 (Jarosz Decl.) at Appendix 28.

Not Inherently Obvious That One Drop of 0.025% Brimonidine Would Reduce Eye Redness

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Not Inherently Obvious That One Drop of 0.025% Brimonidine Would Reduce Eye Redness

- Teaching away and objective evidence of nonobviousness
  - the prior art led POSAs to high doses of brimonidine, expecting that low doses would not work to reduce redness, confirming nonobviousness
- Nonobvious invention vitiates position of inherency in the obvious context



"Finally, we reject the Appellants' argument that the unexpected results do not support nonobviousness because they are merely the inherent properties of an otherwise obvious formulation. As indicated, the prior art did not disclose, either explicitly or implicitly, the claimed formulation; rather, it taught away from such a formulation. A person of ordinary skill in the art thus would not have had a reason to select the claimed formulation from the prior art ranges or to modify Lumigan 0.03% to arrive at the claimed formulation. The unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness."

Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1307 (Fed. Cir. 2015)

245 IPR: Paper 25 at 38-40, Paper 72 at 24-25;
600 IPR: Paper 25 at 34, Paper 68 at 16-17.

Not Inherently Obvious That One Drop of 0.025% Brimonidine Would Reduce Eye Redness

"As we concluded ***in the earlier dispute*** regarding claim 4 of the '149 patent, ***the concomitant administration of brimonidine and timolol ophthalmic composition twice daily is*** obvious in view of the prior art. ***Each asserted claim, however, expressly recites an additional efficacy limitation that further restricts the method*** of administering the composition twice daily: (1) "without loss of efficacy" in claim 4 of the '149 patent; (2) "a therapeutically effective amount" in claim 1 of the '976 patent; and (3) "reduc[ing] the incidence of one or more adverse events" in claim 1 of the '425 patent. Those efficacy limitations are not disclosed by any prior art reference in the record. To the contrary, the prior art shows that the combination dosed twice daily produces a loss of efficacy in the afternoon. The efficacy limitations are also not inherent in the administration of the ophthalmic composition, a finding adequately supported by the record."

Allergan Sales, LLC v. Sandoz, Inc., 717 F. App'x 991, 994 (Fed. Cir. 2017)

245 IPR: Paper 72 at 25; 600 IPR: Paper 68 at 17.