Slayback Pharma

SLAYBACK PHARMA LLC
v.
EYE THERAPIES, LLC

IPR2022-00142

U.S. Patent No. 8,293,742

Oral Hearing
February 27, 2023

Slayback Pharma LLC
Petitioner's Demonstratives.001

Introduction

The Board Should Find All Challenged Claims Unpatentable

- **Ground 1:** Gil (the ’553 patent) anticipates claims 1–2
  - Example 1 discloses a clinical study in which radial keratotomy patients were to be treated with brimonidine to reduce neurogenic inflammation
    - Administration of brimonidine (a vasoconstrictor) reduces redness
    - “about 0.025%” includes 0.03% brimonidine—the concentration administered in Example 1
    - “ocular condition” includes radial keratotomy, but even if it does not, the radial keratotomy procedure necessarily causes redness via neurogenic inflammation
- **Ground 2:** Walters anticipates claims 1–2

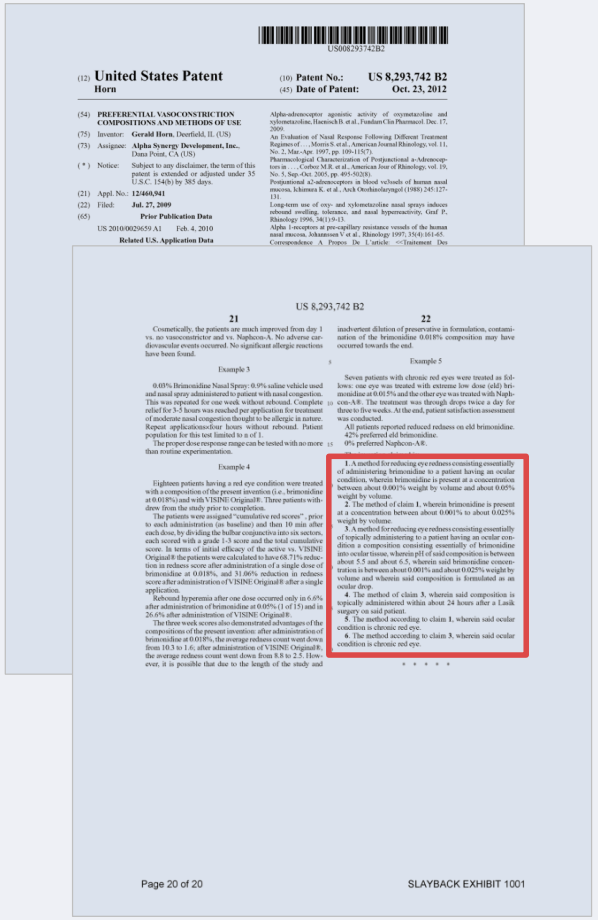
Petition (Paper 2) at 32–44; Reply (Paper 43) at 7–9; Gil (EX-1004); Walters (EX-1005).

The Board Should Find All Challenged Claims Unpatentable

- **Ground 3:** Claims 1-6 are invalid because it would have been obvious to combine:
  - Low dose brimonidine (e.g., Gil)
  - For the reduction of eye redness (e.g., Gil, Norden 2002)
  - Formulated at the known, commercially available pH levels (e.g., Alphagan®)
  - In patients with various causes of eye redness (e.g., Gil, Norden 2002)
- Secondary considerations do not support a finding of non-obviousness

Petition (Paper 2) at 50–64; Reply (Paper 43) at 9–26, Gil (EX-1004); Norden (EX-1002).

Claims of the ’742 Patent



US008293742B2

(12) **United States Patent**
Horn

(10) **Patent No.: US 8,293,742 B2**
(45) **Date of Patent: Oct. 23, 2012**

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

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

(73) Assignee: **Alpha Synergy Development, Inc.**, Dana Point, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 385 days.

(21) Appl. No.: **12/460,941**

(22) Filed: **Jul. 27, 2009**

(65) **Prior Publication Data**

US 2010/0029659 A1 Feb. 4, 2010

Related U.S. Application Data

Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline, Haeinsch B. et al., Fundam Clin Pharmacol. Dec. 17, 2000.

An Evaluation of Nasal Response Following Different Treatment Regimes of . . ., Morris S. et al., American Journal Rhinology, vol. 11, No. 2, Mar.-Apr. 1997, pp. 109-115(7).

Pharmacological Characterization of Postjunctional a-Adrenoceptors in . . ., Corboz M.R. et al., American Jour of Rhinology, vol. 19, No. 5, Sep.-Oct. 2005, pp. 495-502(8).

Postjunctional a2-adrenoceptors in blood vessels of human nasal mucosa, Ichimura K. et al., Arch Otorhinolaryngol (1988) 245:127-131.

Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. Graf P., Rhinology 1996, 34(1):9-13.

Alpha 1-receptors at pre-capillary resistance vessels of the human nasal mucosa, Johannsen V et al., Rhinology 1997, 35(4):161-65.

Correspondence A Propos De L'article: <<Traitement Des

US 8,293,742 B2

21

Cosmetically, the patients are much improved from day 1 vs. no vasoconstrictor and vs. Naphcon-A. No adverse cardiovascular events occurred. No significant allergic reactions have been found.

Example 3

0.03% Brimonidine Nasal Spray: 0.9% saline vehicle used and nasal spray administered to patient with nasal congestion. This was repeated for one week without rebound. Complete relief for 3-5 hours was reached per application for treatment of moderate nasal congestion thought to be allergic in nature. Repeat applications/four hours without rebound. Patient population for this test limited to n of 1.

The proper dose response range can be tested with no more than routine experimentation.

Example 4

Eighteen patients having a red eye condition were treated with a composition of the present invention (i.e., brimonidine at 0.018%) and with VISINE Original®. Three patients withdrew from the study prior to completion.

The patients were assigned "cumulative red scores", prior to each administration (as baseline) and then 10 min after each dose, by dividing the bulbar conjunctiva into six sectors, each scored with a grade 1-3 score and the total cumulative score. In terms of initial efficacy of the active vs. VISINE Original® the patients were calculated to have 68.71% reduction in redness score after administration of a single dose of brimonidine at 0.018%, and 31.06% reduction in redness score after administration of VISINE Original® after a single application.

Rebound hyperemia after one dose occurred only in 6.6% after administration of brimonidine at 0.05% (1 of 15) and in 26.6% after administration of VISINE Original®.

The three week scores also demonstrated advantages of the compositions of the present invention: after administration of brimonidine at 0.018%, the average redness count went down from 10.3 to 1.6; after administration of VISINE Original®, the average redness count went down from 8.8 to 2.5. However, it is possible that due to the length of the study and

22

inadvertent dilution of preservative in formulation, contamination of the brimonidine 0.018% composition may have occurred towards the end.

Example 5

Seven patients with chronic red eyes were treated as follows: one eye was treated with extreme low dose (eld) brimonidine at 0.015% and the other eye was treated with Naphcon-A®. The treatment was through drops twice a day for three to five weeks. At the end, patient satisfaction assessment was conducted.

All patients reported reduced redness on eld brimonidine.

42% preferred eld brimonidine.

0% preferred Naphcon-A®.

1. A method for reducing eye redness consisting essentially of administering brimonidine to a patient having an ocular condition, wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume.

2. The method of claim 1, wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume.

3. A method for reducing eye redness consisting essentially of topically administering to a patient having an ocular condition a composition consisting essentially of brimonidine into ocular tissue, wherein pH of said composition is between about 5.5 and about 6.5, wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume and wherein said composition is formulated as an ocular drop.

4. The method of claim 3, wherein said composition is topically administered within about 24 hours after a Lasik surgery on said patient.

5. The method according to claim 1, wherein said ocular condition is chronic red eye.

6. The method according to claim 3, wherein said ocular condition is chronic red eye.

* * * * *

Page 20 of 20

SLAYBACK EXHIBIT 1001

The invention claimed is:

1. A method for reducing eye redness consisting essentially of administering brimonidine to a patient having an ocular condition, wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume.

2. The method of claim **1**, wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume.

3. A method for reducing eye redness consisting essentially of topically administering to a patient having an ocular condition a composition consisting essentially of brimonidine into ocular tissue, wherein pH of said composition is between about 5.5 and about 6.5, wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume and wherein said composition is formulated as an ocular drop.

4. The method of claim **3**, wherein said composition is topically administered within about 24 hours after a Lasik surgery on said patient.

5. The method according to claim **1**, wherein said ocular condition is chronic red eye.

6. The method according to claim **3**, wherein said ocular condition is chronic red eye.

Reducing redness with low concentrations of brimonidine

pH between about 5.5 and about 6.5

Chronic red eye & after LASIK surgery

’742 Patent (EX-1001).

Anticipation

Gil Anticipates Claims 1 and 2 of the ’742 Patent

The ’742 Patent	Gil (’553 Patent)
[1.preamble] A method for reducing eye redness	
[1.1] consisting essentially of administering brimonidine	UNDISPUTED
[1.2] to a patient having an ocular condition	
[1.3] wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume	UNDISPUTED
[2.1] wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume	

Reply (Paper 43) at 7; Gil (EX-1004).

Gil Discloses a Method for Reducing Eye Redness

- Gil discloses the administration of low concentrations of brimonidine to treat pain and ocular inflammation

EXAMPLE 1

A clinical study is performed to compare the analgesic effect of topically administered brimonidine and placebo following radial keratotomy surgery. One hundred and twenty-four male and female subjects, 21 to 45 years of age, undergo routine, elective, unilateral radial keratotomy for 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.

Efficacy is assessed by evaluation of pain intensity, pain relief, subjective global analgesic efficacy. Symptoms of ocular inflammation (burning/stinging, tearing, etc.) are also recorded.

The results of this study show greater pain relief at hours 2, 3 and 4 in the brimonidine group over the group treated with placebo. This appears to suggest that brimonidine, administered preoperatively, blocks the perception of pain.

Gil (EX-1004) at 4:45–5:2.

FIELD OF THE INVENTION

This invention relates to the topical application of brimonidine for treating ocular pain and neurogenic inflammation and compositions useful for such application.

BACKGROUND OF THE ART

Pain is a well known phenomenon as an indicator of injury or tissue damage due to inflammation, ischemia, mechanical or other irritation.

Gil (EX-1004) at 1:10–19.

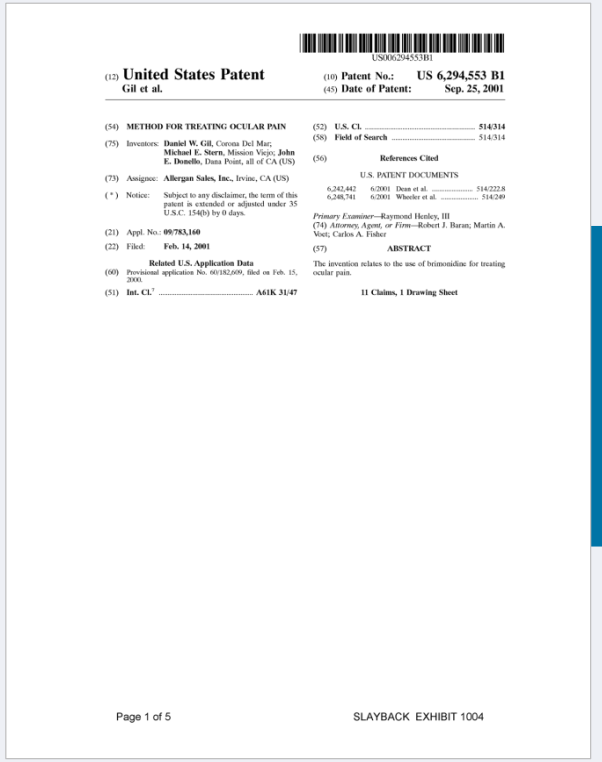
Efficacy is assessed by evaluation of pain intensity, pain relief, subjective global analgesic efficacy. Symptoms of ocular inflammation (burning/stinging, tearing, etc.) are also recorded.

Gil (EX-1004) at 4:62–65.

Petition (Paper 2) at 32; Reply (Paper 43) at 8; Sher Reply Decl. (EX-1049) ¶ 55.

Gil Discloses a Method for Reducing Eye Redness

- Gil's Example 1 discloses a clinical study of ***0.03% brimonidine*** before and after radial keratotomy



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**

(75) Inventors: **Daniel W. Gil**, Corona Del Mar; **Michael E. Stern**, Mission Viejo; **John E. Donello**, Dana Point, all of CA (US)

(73) Assignee: **Allergan Sales, 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 0 days.

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

(22) Filed: **Feb. 14, 2001**

Related U.S. Application Data

(60) Provisional application No. 60/182,609, filed on Feb. 15, 2000.

(51) **Int. Cl.**[7] **A61K 31/47**

(52) **U.S. Cl.** **514/314**

(58) **Field of Search** 514/314

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,242,442 6/2001 Dean et al. 514/222.8
6,248,741 6/2001 Wheeler et al. 514/249

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Robert J. Baran; Martin A. Voet; Carlos A. Fisher

(57) **ABSTRACT**

The invention relates to the use of brimonidine for treating ocular pain.

11 Claims, 1 Drawing Sheet

Page 1 of 5

SLAYBACK EXHIBIT 1004

Includes 124 patients undergoing unilateral radial keratotomy

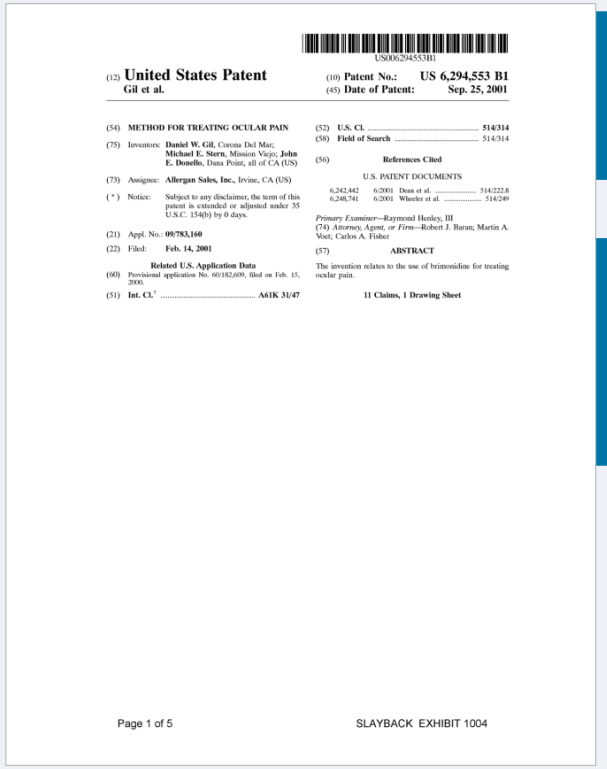
A clinical study is performed to compare the analgesic effect of topically administered brimonidine and placebo following radial keratotomy surgery. One hundred and twenty-four male and female subjects, 21 to 45 years of age, undergo routine, elective, unilateral radial keratotomy for the correction of myopia and brimonidine is administered as a 0.03% ophthalmic solution.

Gil (EX-1004) at 4:46–53.

Petition (Paper 2) at 33–34; Reply (Paper 43) at 8–9.

Gil Discloses a Method for Reducing Eye Redness

- Ocular inflammation is a proximal cause of pain and eye redness



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

(75) Inventors: **Daniel W. Gil**, Corona Del Mar; **Michael E. Stern**, Mission Viejo; **John E. Donello**, Dana Point, all of CA (US)

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

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(58) **Field of Search** 514/314

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6,248,741 6/2001 Wheeler et al. 514/249

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Robert J. Baran; Martin A. Voet; Carlos A. Fisher

(57) **ABSTRACT**

The invention relates to the use of brimonidine for treating ocular pain.

11 Claims, 1 Drawing Sheet

Page 1 of 5

SLAYBACK EXHIBIT 1004

1. Activation of primary afferents (neurons)

2. Release of neuropeptides → neurogenic inflammation

The first step leading to the sensation of pain is the activation of nociceptive primary afferents by intense thermal, mechanical or chemical stimuli. Indirect studies of

* * *

The stimulation of primary afferents leads to action potentials in their axons which propagate to the spinal cord. In addition, excited primary afferents release neuropeptides (substance P, calcitonin gene-related peptide, neurokinin A) at their peripheral terminals. Neuropeptides enhance inflammatory reactions in the injured tissue, contributing to vasodilation, edema, and increased vascular permeability, this phenomenon is called 'neurogenic inflammation'.

Gil (EX-1004) at 1:2–43.

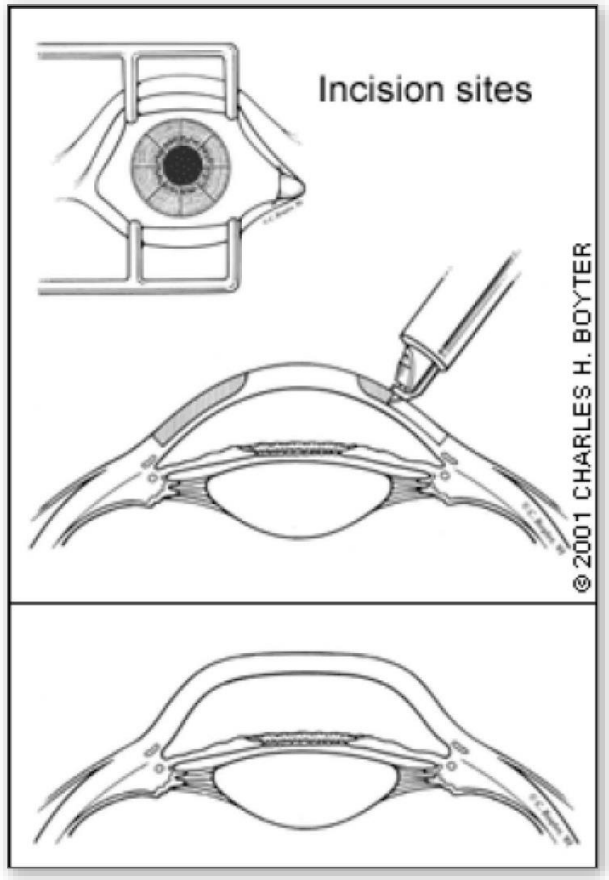
Ocular responses characteristic of neurogenic inflammation, including redness and pupillary constriction, are also observed in rabbits following external stimuli. The

Gil (EX-1004) at 5:39–41.

Reply (Paper 43) at 8–9; Sher Reply Decl. (EX-1049) ¶¶ 48–55.

Radial Keratotomy Necessarily Causes Eye Redness

- Lid speculum mechanically forces the eyelids to remain open
- Surgeon makes numerous incisions to the cornea
- Corneal incisions result in tissue damage
- Tissue damage triggers inflammatory cascade (release of inflammatory mediators)
- Inflammatory cascade results in redness and pain (vasodilation of the nearby blood vessels)



Noecker Decl. (EX-2020) ¶ 104.

Reply (Paper 43) at 8–9; Sher Reply Decl. (EX-1049) ¶¶ 45–50.

Radial Keratotomy Necessarily Causes Eye Redness

DR. SHER:

on "ocular condition." Additionally, and as discussed in more detail below, in my experience, all radial keratotomy patients have some degree of eye redness after the procedure. Therefore, even under Dr. Noecker's construction of this term, radial keratotomy would still be an "ocular condition" of the claims.

Sher Reply Decl. (EX-1049) ¶ 40.

THE WITNESS: As -- as I detailed in my declaration and based on my experience in RK surgery or -- AK surgery is no different, I have never seen a patient who I've cut the cornea on or for that matter done cataract surgery on or any of these procedures who have not had some eye redness, some tearing, some irritation symptoms after the surgical procedure. That's my experience.

Sher Dep. Tr. (EX-2213) at 35:1–10.

Petition (Paper 2) at 34; Reply (Paper 43) at 8–9.

The Natural Result of Administering Low Concentrations of Brimonidine to Radial Keratotomy Patients Is Reduced Redness

"In general, a limitation or the entire invention is inherent and in the public domain if it is the 'natural result flowing from' the explicit disclosure of the prior art."

Schering Corp. v. Geneva Pharms., 339 F.3d 1373, 1379 (Fed. Cir. 2003) (citing *Eli Lilly & Co. v. Barr Laby's, Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)).

Reply (Paper 43) at 8.

Administering Brimonidine 0.03% to Patients Undergoing Radial Keratotomy Necessarily Reduces Eye Redness

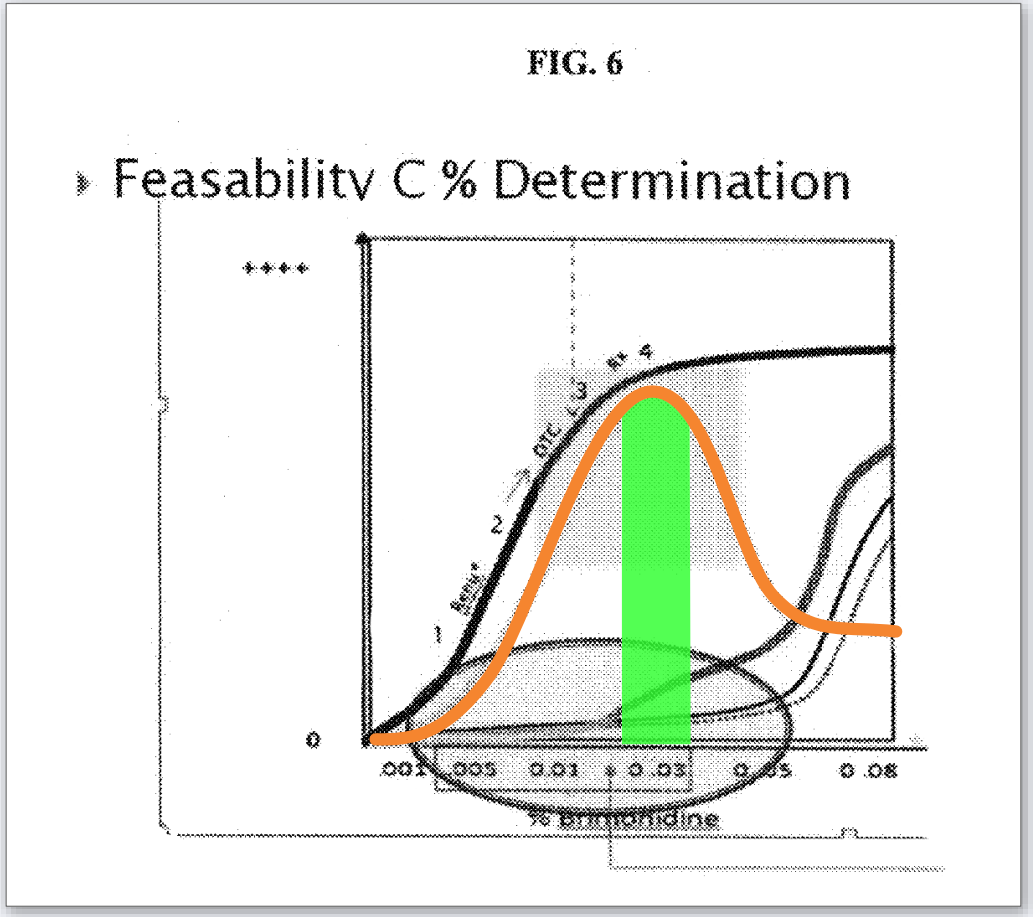


FIG. **6** depicts a graphical representation of a finding of the present invention that an increased rebound hyperemia begins at around 0.03% for brimonidine. It thus demonstrates that the net effectiveness of brimonidine as a decongestant is greatest between about 0.01% and about 0.03%; preferably, between about 0.012% and about 0.02%

FIG. **4**E shows the effect of brimonidine at 0.033% on the left eye only, 4 hrs after the effect shown in FIG. **4**D (showing the third application to be without rebound hyperemia).

'742 Patent (EX-1001) at 19:52–57, 20:17–19.

Petition (Paper 2) at 30; Reply (Paper 43) at 9.

Gil Discloses a Method for Reducing Eye Redness

- The challenged claims contain no efficacy limitation.

> Based on the foregoing and our review of the record as a whole, we find no persuasive support for construing the preamble recitation of a "method for treating a patient with an angiogenic eye disorder" as requiring such "treating" to achieve any particular level of effectiveness, much less a "high level of efficacy." Rather, as discussed above, we find that the evidence of record and the Specification support construing the phrase as meaning administering a compound, i.e., the recited VEGF antagonist, to such patient for the purpose of improving or providing a beneficial effect in their angiogenic eye disorder.

Mylan Pharms. Inc. v. Regeneron Pharms., Inc.,
No. IPR2021-00881, 2022 WL 16842073, at *11 (P.T.A.B. Nov. 9, 2022).

Reply (Paper 43) at 7–8.

Gil Anticipates Claims 1 and 2 of the ’742 Patent

The ’742 Patent	Gil (’553 Patent)
[1.preamble] A method for reducing eye redness	
[1.1] consisting essentially of administering brimonidine	UNDISPUTED
[1.2] to a patient having an ocular condition	
[1.3] wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume	UNDISPUTED
[2.1] wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume	

Petition (Paper 2) at 33–34; Reply (Paper 43) at 8–9; Gil (EX-1004).

Claim Construction – “ocular condition”

Petitioner’s Construction	Patent Owner’s Construction
“ocular condition” includes, without limitation: eye redness; glaucoma (including open-angle glaucoma); elevated intraocular pressure, also known as ocular hypertension; postoperative reduction of subconjunctival hemorrhage and hyperemia after refractive surgery such as LASIK and radial keratotomy; subconjunctival hemorrhage and hyperemia prophylaxis prior to refractive surgery such as LASIK and radial keratotomy; and redness in the eye following LASIK or radial keratotomy.	a condition of the eye causing ocular hyperemia that can be reduced • Not subconjunctival hemorrhage • Not effects of radial keratotomy

Petition (Paper 2) at 31; Reply (Paper 43) at 1–2; PO Resp. (Paper 30) at 25–27.

Radial Keratotomy Results in Ocular Conditions

b) Ocular Conditions

Ocular conditions include, but are not limited to, red eye, including chronic red eye; ocular vascular congestion after Lasik surgery; prophylactic intraoperative and postoperative reduction of hemorrhage and hyperemia after Lasik surgery; preoperative hemorrhage and hyperemia prophylaxis prior to Lasik surgery; prophylactic diabetic retinopathy; macular edema such as that associated with diabetes; conditions of retinal degeneration such as glaucoma, macular degeneration such as age-related macular degeneration (ARMD) and retinitis.pigmentosa; retinal dystrophies; elevated baseline hyperemia in glaucoma patients; inflammatory disorders of the retina; vascular occlusive conditions of the retina such as retinal vein occlusions or branch or central retinal artery occlusions; retinopathy of prematurity; retinopathy associated with blood disorders such as sickle cell anemia; elevated intraocular pressure; ocular itch; damage following retinal detachment; damage or insult due to vitrectomy, retinal or other surgery; and other retinal damage including therapeutic damage such as that resulting from laser treatment of the retina, for example, pan-retinal photocoagulation for diabetic retinopathy or photodynamic therapy of the retina. Ocular conditions that can be prevented or alleviated by administering the topical formulations of the present invention further include, without limitation, generic and acquired optic neuropathies such as optic neuropathies characterized primarily by loss of central vision, for example, Leber's hereditary optic neuropathy (LEON), autosomal dominant optic atrophy (Kjer disease) and other optic neuropathies such as those involving mitochondrial defects aberrant dynamin-related proteins or inappropriate apoptosis; and optic neuritis such as that associated with multiple sclerosis, retinal vein occlusions or photodynamic or laser therapy. See, for example, Carelli et al., Neurochem. Intl. 40:573-584 (2002); and Olichon et al., J. Biol. Chem. 278:7743-7746 (2003). The term "ocular condition" also encompasses aesthetic conditions, for example, excessive redness of an eye. The methods and compositions

including chronic red eye; ocular vascular congestion after Lasik surgery; prophylactic intraoperative and postoperative reduction of hemorrhage and hyperemia after Lasik surgery; preoperative hemorrhage and hyperemia prophylaxis prior to Lasik surgery; prophylactic diabetic retinopathy; macular

* * *

detachment; damage or insult due to vitrectomy, retinal or other surgery; and other retinal damage including therapeutic

* * *

Biol. Chem. 278:7743-7746 (2003). The term "ocular condition" also encompasses aesthetic conditions, for example, excessive redness of an eye. The methods and compositions

'742 Patent (EX-1001) at 12:13–49.

Petition (Paper 2) at 25, 31; Reply (Paper 43) at 1–2; Sher Reply Decl. (EX-1049) ¶¶ 38–40.

Ocular Condition Is Not Limited to Conditions that Cause Ocular Hyperemia

b) Ocular Conditions

Ocular conditions include, but are not limited to, red eye, including chronic red eye; ocular vascular congestion after Lasik surgery; prophylactic intraoperative and postoperative reduction of hemorrhage and hyperemia after Lasik surgery; preoperative hemorrhage and hyperemia prophylaxis prior to Lasik surgery; prophylactic diabetic retinopathy; macular edema such as that associated with diabetes; conditions of retinal degeneration such as glaucoma, macular degeneration such as age-related macular degeneration (ARMD) and retinitis.pigmentosa; retinal dystrophies; elevated baseline hyperemia in glaucoma patients; inflammatory disorders of the retina; vascular occlusive conditions of the retina such as retinal vein occlusions or branch or central retinal artery occlusions; retinopathy of prematurity; retinopathy associated with blood disorders such as sickle cell anemia; elevated intraocular pressure; ocular itch; damage following retinal detachment; damage or insult due to vitrectomy, retinal or other surgery; and other retinal damage including therapeutic damage such as that resulting from laser treatment of the retina, for example, pan-retinal photocoagulation for diabetic retinopathy or photodynamic therapy of the retina. Ocular conditions that can be prevented or alleviated by administering the topical formulations of the present invention further include, without limitation, generic and acquired optic neuropathies such as optic neuropathies characterized primarily by loss of central vision, for example, Leber's hereditary optic neuropathy (LEON), autosomal dominant optic atrophy (Kjer disease) and other optic neuropathies such as those involving mitochondrial defects aberrant dynamin-related proteins or inappropriate apoptosis; and optic neuritis such as that associated with multiple sclerosis, retinal vein occlusions or photodynamic or laser therapy. See, for example, Carelli et al., Neurochem. Intl. 40:573-584 (2002); and Olichon et al., J. Biol. Chem. 278:7743-7746 (2003). The term "ocular condition" also encompasses aesthetic conditions, for example, excessive redness of an eye. The methods and compositions

"Ocular Condition" includes:

Eye conditions that do not cause redness

- Diabetic retinopathy
- Macular degeneration
- Glaucoma
- Retinal artery occlusion
- Retinal detachment

Hemorrhages

- Prophylactic intraoperative and postoperative reduction of hemorrhage after Lasik surgery
- Preoperative hemorrhage prophylaxis prior to Lasik surgery

Reply (Paper 43) 1–2; Sher Reply Decl. (EX-1049) ¶¶ 36, 38.

Gil Anticipates Claims 1 and 2 of the ’742 Patent

The ’742 Patent	Gil (’553 Patent)
[1.preamble] A method for reducing eye redness	✓
[1.1] consisting essentially of administering brimonidine	UNDISPUTED
[1.2] to a patient having an ocular condition	✓
[1.3] wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume	UNDISPUTED
[2.1] wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume	

Petition (Paper 2) at 33–36; Reply (Paper 43) at 8–9; Gil (EX-1004).

Claim Construction – “about 0.025%”

Petitioner’s Construction	Results of Patent Owner’s Construction
“about 0.025%” includes 0.03%	“about 0.025%” excludes 0.03%

Petition (Paper 2) at 27–31; Reply (Paper 43) at 2–7; PO Resp. (Paper 30) at 27–36.

The Use of the Word "About" Avoids a Strict Numerical Boundary

> "When 'about' is used as part of a numeric range, 'the use of the word 'about' avoids a strict numerical boundary to the specified parameter.'"

Cohesive Techs. v. Waters Corp., 543 F.3d 1351, 1368 (Fed. Cir. 2008).

> "Under *Cohesive*, claim construction of 'about 0.025%' in this IPR 'must focus . . . on the criticality of the [numerical limitation] to the invention.'"

Petition (Paper 2) at 28 (quoting *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Lab'ys, Ltd.*, 476 F.3d 1321,1327 (Fed. Cir. 2007) (ellipses and bracketed language by the Federal Circuit in *Cohesive*)).

> "The relevant inquiry 'is the purpose of the *limitation* in the claimed invention.'"

Petition (Paper 2) at 28 (quoting *Ortho-McNeil*, 476 F.3d at 1327 (italics in original)).

Petition (Paper 2) at 27–28.

The Specification Does Not Show "About 0.025%" Is Critical

For purposes of the present invention, the terms below are defined as follows.

The term "low concentrations" refers to concentrations from between about 0.0001% to about 0.05%; more preferably, from about 0.001% to about 0.025%; even more preferably, from about 0.01% to about 0.025%; and even more preferably, from about 0.01% to about 0.02% weight by volume.

'742 Patent (EX-1001) at 3:58–65.

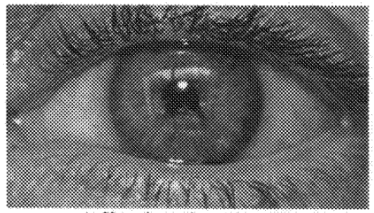
When the methods and compositions of the present invention are used in conjunction with Lasik surgery, the preferred a-2 agonist is brimonidine at a concentration of from about 0.015% to about 0.05%, and more preferably, from about

'742 Patent (EX-1001) at 12:60–63.

For the methods of scleral whitening, the preferred a-2 agonist is brimonidine at a concentration of from about 0.01% to about 0.05%, and more preferably, from about 0.015% to

'742 Patent (EX-1001) at 14:14–16.

Fig 4e: Brimonidine 0.033% OS only; 4 hours after 4d



(effect lasted ~ 4 hours)

Vs. Baseline 11 hours earlier:

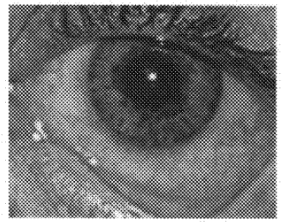


FIG. 4E

'742 Patent (EX-1001) at Fig. 4E.

FIG. **6** depicts a graphical representation of a finding of the present invention that an increased rebound hyperemia begins at around 0.03% for brimonidine. It thus demonstrates that the net effectiveness of brimonidine as a decongestant is greatest between about 0.01% and about 0.03%; preferably, between about 0.012% and about 0.02%

'742 Patent (EX-1001) at 19:52–57.

Petition (Paper 2) at 27–31; '742 Patent (EX-1001) at Abstract, 3:30–33, 5:52–54, 9:11–14:6; Laskar Decl. (EX-1003) ¶¶ 65, 67–73.

The Prosecution History Confirms that the Applicants Did Not Intend to Exclude 0.03%

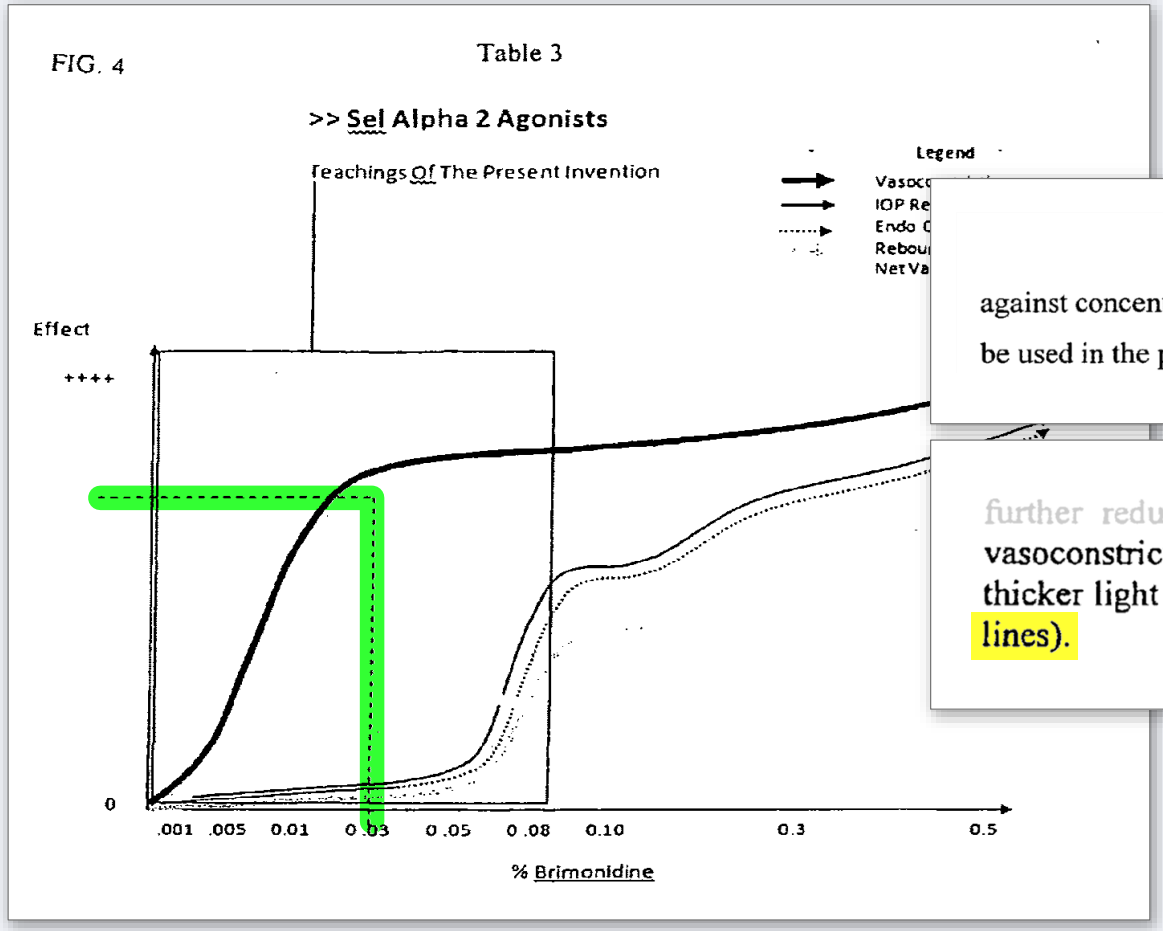


Fig. 4 is a graphical depiction (*Table 3*) of the variation of clinical effectiveness against concentration for compositions comprising the alpha 2 agonist brimonidine which may be used in the present invention providing at lower concentrations than shown in Fig. 3

further reduction in concentration (black solid light gray curve). The net vasoconstrictive effect curve (vasoconstriction – rebound) is shown by the thicker light gray curve, and peaks at ~ 0.025% +/- 0.01% (intersecting dashed lines).

'481 Provisional (EX-1011) at 68, 111.

Reply (Paper 43) at 4–5; Laskar Reply Decl. (EX-1048) ¶ 16; Sher Reply Decl. (EX-1049) ¶ 22.

Patent Owners Arguments All Fail

- The patentee did not act as lexicographers to define "about 0.025%" as excluding 0.03%
- The specification does not "clinically distinguish" 0.025% from 0.03%"
- There is no basis to use extrinsic evidence to import a ± 10% limitation into the meaning of "about"

Reply (Paper 43) at 2–7.

The Patentee Was Not Its Own Lexicographer

PATENT OWNER CLAIMS:

> 0.025%. (Petition at 27.) *First*, doing so ignores that Patentee was his own lexicographer and defined 0.025% as separate from 0.03%, which is improper.

PO Resp. (Paper 30) at 30.

> "To act as its own lexicographer, a patentee must clearly set forth a definition of the disputed claim term" and must "clearly express an intent to redefine the term."

Hill-Rom Servs., Inc. v. Stryker Corp., 755 F.3d 1367, 1371 (Fed. Cir. 2014).

Reply (Paper 43) at 2–4; PO Resp. (Paper 30) at 27–29; '742 Patent (EX-1001) at 3:55–4:24, 8:46–55, 8:56–63; Laskar Reply Decl. (EX-1048) ¶¶ 7–13; Williams Dep. Tr. (EX-1054) at 26:2–14.

The Patentee Was Not Its Own Lexicographer

- Listing preferred embodiments ***is not*** lexicography

Micron Tech., Inc. v. Lone Start Silicon Innovations LLC, No. IPR2017-01562, 2018 WL 6602102, at *4–*5 (P.T.A.B. Dec. 13, 2018).

In a preferred embodiment, the invention generally relates to a method of reducing capillary permeability in a pulmonary condition associated with swollen nasal turbinates comprising administering to a patient in need thereof a composition consisting essentially of brimonidine, wherein pH of said composition is between about 5.0 and about 6.5, wherein said brimonidine concentration is from between about 0.001% to about 0.025% weight by volume, and wherein said composition is formulated as an aerosolized composition and administered into a nasal airway of the patient.

In another embodiment, the invention generally relates to a method of treating respiratory syncytial virus (RSV) bronchitis comprising administering to a patient in need thereof a composition consisting essentially of brimonidine, wherein pH of said composition is between about 5.0 and about 6.5, wherein said brimonidine concentration is from between about 0.001% to about 0.07%, more preferably, from between about 0.001% to about 0.03% weight by volume.

Method of reducing capillary permeability in pulmonary condition associated with swollen nasal turbinates

Method of treating respiratory syncytial virus (RSV) bronchitis

'742 Patent (EX-1001) at 8:46–63.

Reply (Paper 43) at 3.

The Specification Does Not "Clinically Distinguish" 0.025% from 0.03%

Figure 2

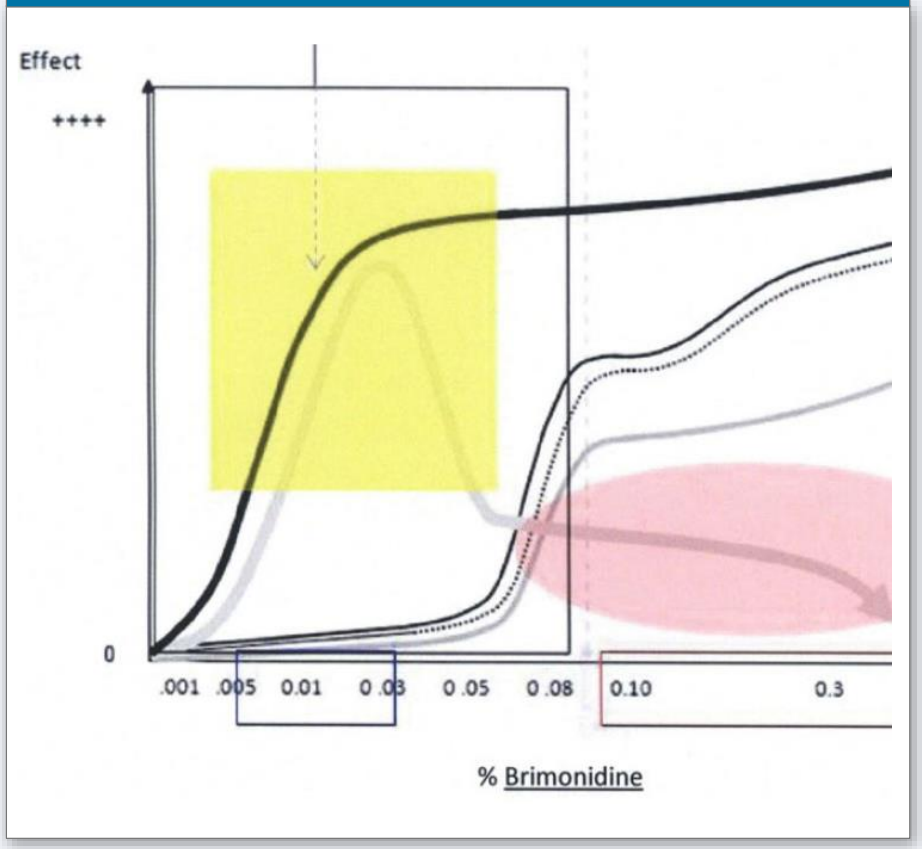
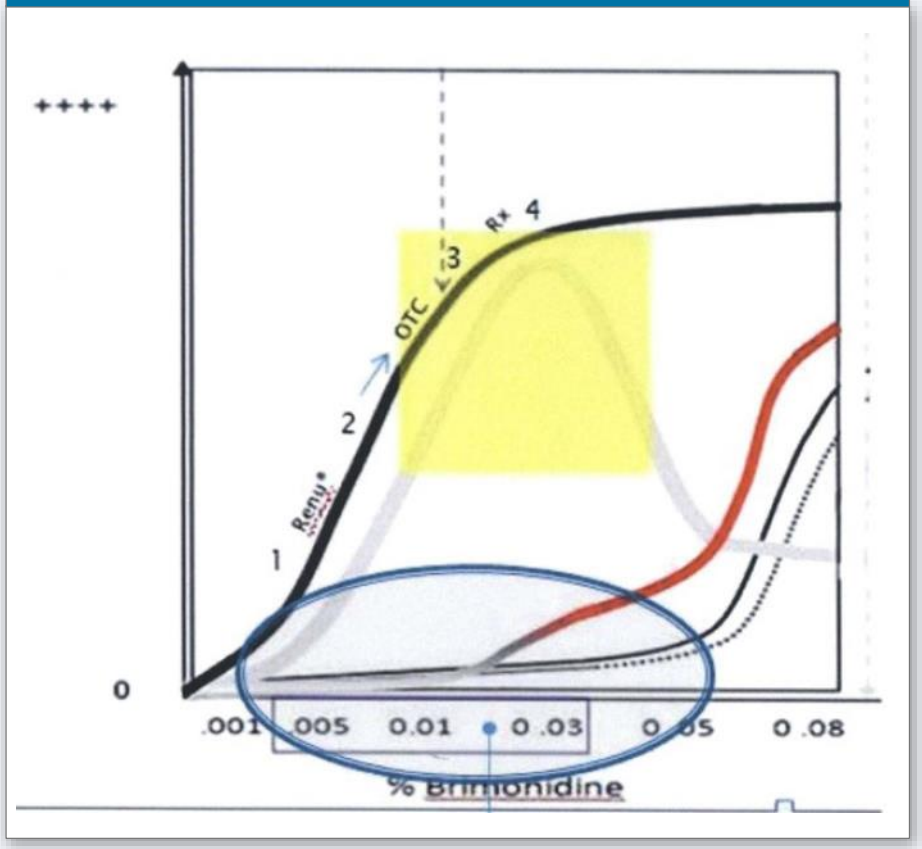
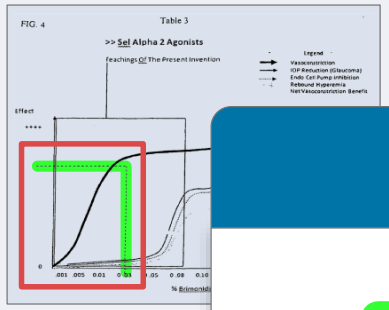


Figure 6



Reply (Paper 43) at 5–6.

The Specification Does Not Convey The "Criticality" Of 0.025%



'481 Provisional
(EX-1011)

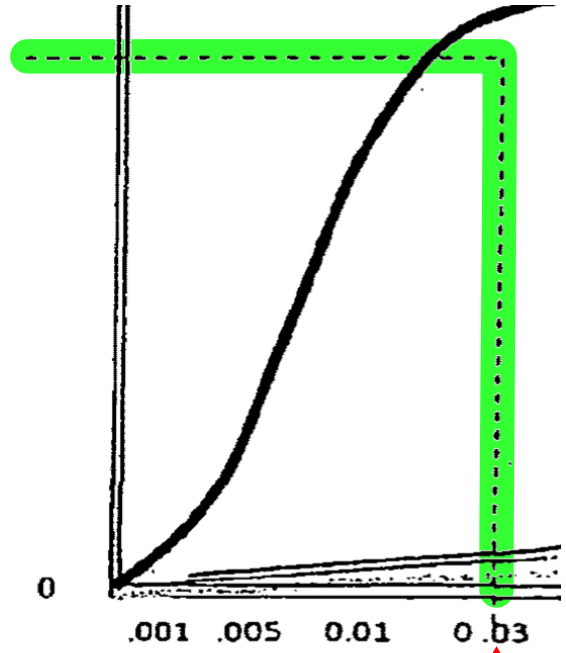
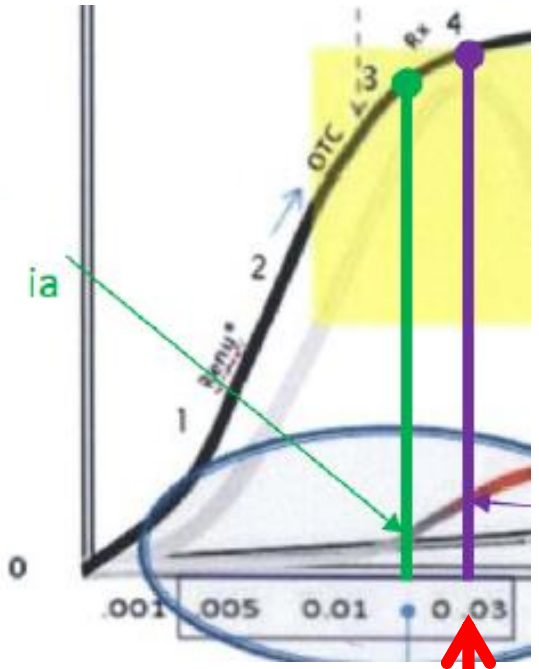
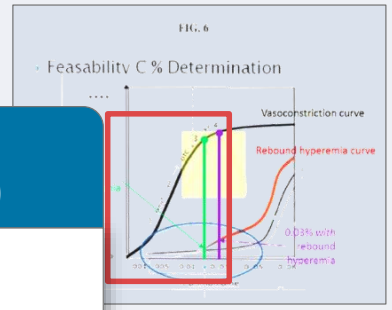


Figure 6
(annotated by Noecker, EX-2020)





0.025% in '481 Provisional… | …is at same position as… | …0.03% in Noecker's Decl.

Reply (Paper 43) at 5; Sher Reply Decl. (EX-1049) ¶¶ 22, 28.

It Would Be Improper To Import a ± 10% Limitation From Extrinsic Evidence

- Nothing in the specification adopts numerical limitations of extrinsic evidence, such as FDA acceptance criteria or the U.S.P.
- If the inventors intended to define “about” with a strict ± 10% limitation, they would have done so.
- FDA acceptance criteria and U.S.P. definitions account for variability and experimental error, not a range of concentrations.

Reply (Paper 43) at 3–4; Laskar Reply Decl. (EX-1048) ¶¶ 7–13.

Gil Anticipates Claims 1 and 2 of the ’742 Patent

The ’742 Patent	Gil (’553 Patent)
[1.preamble] A method for reducing eye redness	✓
[1.1] consisting essentially of administering brimonidine	UNDISPUTED
[1.2] to a patient having an ocular condition	✓
[1.3] wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume	UNDISPUTED
[2.1] wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume	✓

Petition (Paper 2) at 33–37; Reply (Paper 43) at 8–9; Gil (EX-1004).

Ground 1: Anticipated by Gil (the ’553 Patent)

Claim 1 of the ’742 Patent	Gil (the ’553 Patent)
1. A method for reducing eye redness	Express references in Gil to reducing ocular inflammation, i.e., eye redness: • Example 1 intended to reduce inflammation • “Symptoms of ocular inflammation (burning/stinging, tearing, etc.) are also recorded).” Inherent disclosure that administering 0.03% brimonidine would necessarily reduce redness • Radial keratotomy necessarily results in redness • Corneal incision → tissue damage → inflammatory cascade → eye redness (vasodilation of surrounding blood vessels)
consisting essentially of administering brimonidine	“brimonidine is administered”
to a patient having an ocular condition,	“A clinical study is performed to compare the analgesic effect of topically administered brimonidine and placebo following radial keratotomy surgery.” Claim construction: • Specification’s definition of “ocular condition” includes radial keratotomy Radial keratotomy necessarily results in redness
wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume.	“brimonidine is administered as a 0.03% ophthalmic solution”

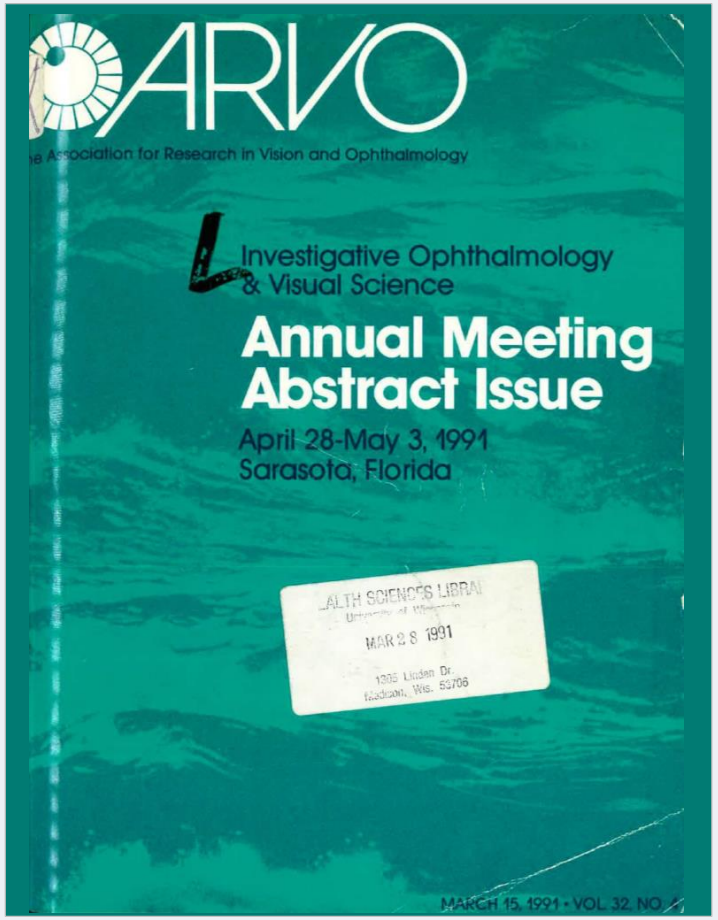
Petition (Paper 2) at 32–37; Reply (Paper 43) at 7–9; Gil (EX-1004).

Ground 1: Anticipated by Gil (the ’553 Patent)

Claim 2 of the ’742 Patent	Gil (the ’553 Patent)
2. The method of claim 1,	(previous slide)
wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume.	“brimonidine is administered as a 0.03% ophthalmic solution” Claim construction: “about 0.025%” includes 0.03%

Petition (Paper 2) at 32–37; Reply (Paper 43) at 7–9; Gil (EX-1004).

Ground 2: Anticipated by Walters 1991



1572 — 9:00

A PILOT STUDY OF THE EFFICACY AND SAFETY OF AGN 190342-LF 0.02% AND 0.08% IN PATIENTS WITH ELEVATED INTRAOCULAR PRESSURE.

Thomas R. Walters,[1] Rex L. Repass,[1] Julia P. Sargent,[1] Elaine P. Kelley,[2] Jack F. Stoecker,[2] Kuankuan S. Chen[2], David G. Harper[2], Biomedical Research Group,[1] Austin, TX., Allergan, Inc.,[2] Irvine, CA.

AGN 190342-LF is a relatively selective alpha$_2$-adrenoceptor agonist under investigation as an ocular hypotensive agent. Structurally similar to clonidine, both compounds possess a 2-amino-imidazoline group. Topically administered, AGN 190342-LF lowers intraocular pressure (IOP) in normotensive and ocular hypertensive monkeys, rabbits, and cats over a dose range of 0.001% to 1%. IOP reduction appears to be produced by a decrease in aqueous humor flow, caused by stimulation of alpha$_2$-adrenoceptors located, in part, on ocular sympathetic nerve endings. In this randomized, double-masked, pilot study, we evaluated the efficacy and safety of bilateral, twice-daily administration of AGN 190342-LF 0.08%, 0.02% or vehicle in 13 patients with open-angle glaucoma or ocular hypertension. Overall mean reductions in IOP were 6.0 mm Hg (23.9%), 3.4 mm Hg (13.8%), and 2.0 mm Hg (7.2%) for the 0.08%, 0.02%, and vehicle groups, respectively, following three days of treatment. Mean decreases in heart rate and blood pressure were not clinically significant. The results of this pilot study indicate that AGN 190342-LF has potential in the treatment of elevated intraocular pressure.

Petition (Paper 2) at 37–44.

Obviousness

Brimonidine Was a Known Vasoconstrictor and Eye Redness Reducer

Gil (the ’553 patent) discloses all the limitations of claims 1-2

- Administration of brimonidine to reduce neurogenic inflammation (redness) in radial keratotomy patients
- Example 4:

> Ocular responses characteristic of neurogenic inflammation, including redness and pupillary constriction, are also observed in rabbits following external stimuli. The ability of an ophthalmic solution of brimonidine at concentrations 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.
>
> Gil (EX-1004) at 5:38-46.

Other prior art references agree that brimonidine was known to reduce redness

- Norden 2002 (EX-1006)
- Robin 1998 (EX-1018)
- Lachkar 1998 (EX-1019)
- U.S. Patent No. 6,242,442 (“Dean”) (EX-1007)
- Wikberg 2001 (EX-1017)
- Alphagan® Label 1998 (EX-1008)

Petition (Paper 2) at 17–19, 21, 33–34; Reply (Paper 43) at 7–9;
Sher Decl. (EX-1002) ¶¶ 30–33, 38, 41, 49–51, 65–67, 82–97,101, 109–10, 112–17,122–25, 132–36.

Claim 3 of the ’742 Patent Is Obvious

The ’742 Patent	Prior Art Ref.’s
[3.preamble] A method for reducing eye redness consisting essentially of	Gil (’553 patent) Norden 2002
[3.1] “topically administering”	Gil (’553 patent) Norden 2002
[3.2] “to a patient having an ocular condition”	Gil (’553 patent) Norden 2002
[3.3] “a composition consisting essentially of brimonidine”	Gil (’553 patent) Norden 2002
[3.4] “into ocular tissue”	Gil (’553 patent) Norden 2002
[3.5] “wherein pH of said composition is between about 5.5 and about 6.5”	Alphagan® Label
[3.6] “wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume”	Gil (’553 patent)

Petition (Paper 2) at 50–56; Sher Decl. (EX-1002) ¶¶ 140–68; Gil (EX-1004); Norden (EX-1006); Alphagan® 1998 Label (EX-1008).

Norden 2002 Discloses Actual Use of Brimonidine to Reduce Eye Redness in LASIK Patients

- Norden 2002 discloses data from a clinical study in which brimonidine was administered prophylactically to patients undergoing LASIK
  - Brimonidine reduced hyperemia compared to placebo

Although two independent clinical studies have shown that topical brimonidine does not significantly alter posterior segment hemodynamics[2,3], the alpha-2 adrenergic agonist drugs as a class are also considered to be strong vasoconstrictors.[4] There are many anecdotal reports that the use of topical brimonidine before laser in situ keratomileusis (LASIK) can help prevent bleeding-related problems in the anterior segment, and some refractive surgeons now administer it prophylactically to reduce subconjunctival hemorrhage and improve the postoperative appearance.

Norden (EX-1006) at 468.

RESULTS: Subconjunctival hemorrhage was observed in 22 of 61 eyes (36.1%). Three of these 22 eyes (13.6%) received prophylactic brimonidine; the remaining 19 eyes with subconjunctival hemorrhage (86.3%) did not receive brimonidine (*P*<.0001). All but three eyes had some hyperemia; however, the amount of hyperemia was lower in the brimonidine group (*P*<.0001). Bleeding from the superior micropannus occurred in four of 61 eyes (6.6%). One of these four eyes received brimonidine. There was one case of flap slippage in a non-brimonidine eye with a nasal hinge; no flap striae were observed after repositioning.

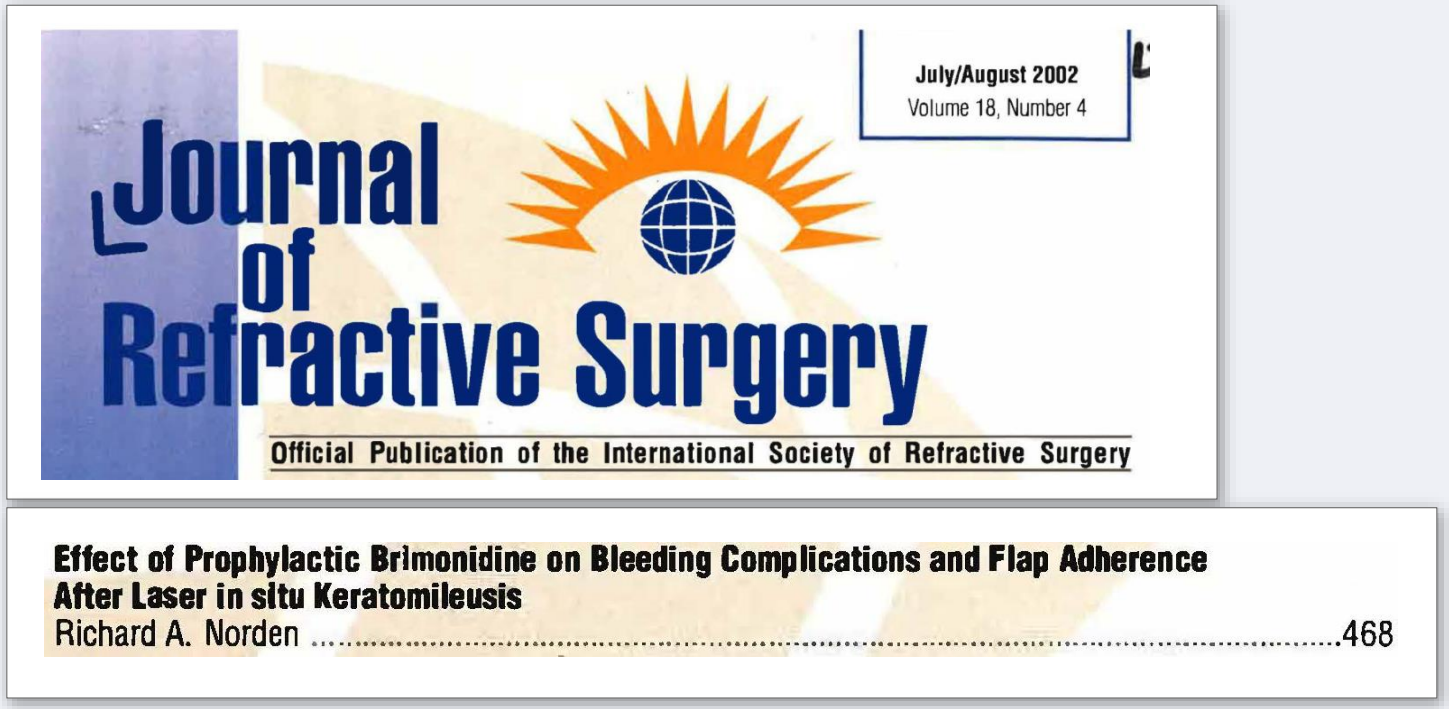
CONCLUSION: This study suggests that brimonidine administered before LASIK may significantly reduce subconjunctival hemorrhage and reduce the amount of hyperemia. [*J Refract Surg* 2002;18:468-471]

Norden (EX-1006) at 468.

Petition (Paper 2) at 18, 21, 51; Sher Decl. (EX-1002) ¶¶ 31–32, 38, 83–84, 112, 143, 152.

Norden 2002 Discloses Actual Use of Brimonidine to Reduce Eye Redness in LASIK Patients

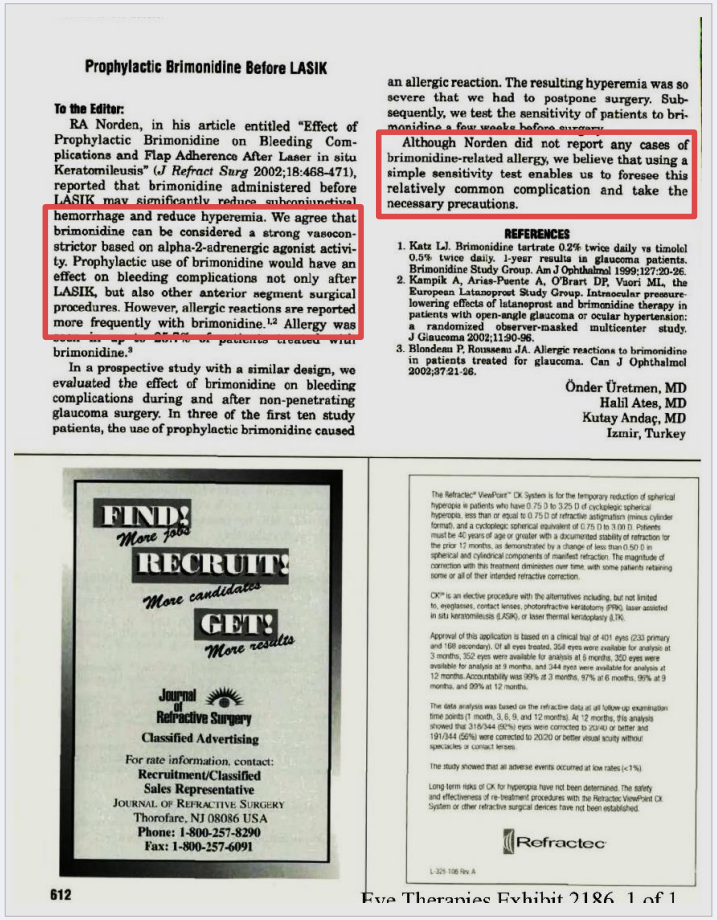
- Norden 2002 was published in a highly respected journal



Norden (EX-1006) at Cover Page.

Petition (Paper 2) at 46; Reply (Paper 43) at 11; Sher Decl. (EX-1002) ¶ 82.

Contemporaneous Reports Did Not Question Norden 2002



Prophylactic Brimonidine Before LASIK

To the Editor:

RA Norden, in his article entitled "Effect of Prophylactic Brimonidine on Bleeding Complications and Flap Adherence After Laser in situ Keratomileusis" (*J Refract Surg* 2002;18:468-471), reported that brimonidine administered before LASIK may significantly reduce subconjunctival hemorrhage and reduce hyperemia. We agree that brimonidine can be considered a strong vasoconstrictor based on alpha-2-adrenergic agonist activity. Prophylactic use of brimonidine would have an effect on bleeding complications not only after LASIK, but also other anterior segment surgical procedures. However, allergic reactions are reported more frequently with brimonidine.[1,2] Allergy was [illegible] of patients treated with brimonidine.[3]

In a prospective study with a similar design, we evaluated the effect of brimonidine on bleeding complications during and after non-penetrating glaucoma surgery. In three of the first ten study patients, the use of prophylactic brimonidine caused an allergic reaction. The resulting hyperemia was so severe that we had to postpone surgery. Subsequently, we test the sensitivity of patients to brimonidine a few weeks before surgery.

Although Norden did not report any cases of brimonidine-related allergy, we believe that using a simple sensitivity test enables us to foresee this relatively common complication and take the necessary precautions.

REFERENCES

1. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily. 1-year results in glaucoma patients. Brimonidine Study Group. Am J Ophthalmol 1999;127:20-26.
2. Kampik A, Arias-Puente A, O'Brart DP, Visori ML, the European Latanoprost Study Group. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. J Glaucoma 2002;11:90-96.
3. Blondeau P, Rousseau JA. Allergic reactions to brimonidine in patients treated for glaucoma. Can J Ophthalmol 2002;37:21-26.

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Eye Therapies Exhibit 2186, 1 of 1

hemorrhage and reduce hyperemia. We agree that brimonidine can be considered a strong vasoconstrictor based on alpha-2-adrenergic agonist activity. Prophylactic use of brimonidine would have an effect on bleeding complications not only after LASIK, but also other anterior segment surgical procedures. However, allergic reactions are reported more frequently with brimonidine.[1,2] Allergy was

* * *

Although Norden did not report any cases of brimonidine-related allergy, we believe that using a simple sensitivity test enables us to foresee this relatively common complication and take the necessary precautions.

Üretmen (EX-2186) at 612.

Reply (Paper 43) at 11; Sher Reply Decl. (EX-1049) ¶¶ 86–88.

Contemporaneous Reports Did Not Question Norden 2002

ARTICLE

Increased risk for flap dislocation with perioperative brimonidine use in femtosecond laser in situ keratomileusis

Gonzalo Muñoz, MD, PhD, FEBO, César Albarrán-Diego, OD, Hani F. Sakla, MD, PhD, Jaime Javaloy, MD, PhD

PURPOSE: To determine whether brimonidine 0.2% minimizes the occurrence of subconjunctival hemorrhages without inducing postoperative flap complications in femtosecond laser in situ keratomileusis (LASIK).

SETTING: Centro Oftalmológico Marqués de Sotelo and Hospital NISA Virgen del Consuelo, Valencia, Spain.

METHODS: This prospective contralateral-eye interventional study evaluated consecutive patients who had bilateral simultaneous femtosecond LASIK for myopia (spherical equivalent [SE] range −1.00 to −8.00 diopters) performed with an IntraLase femtosecond laser and a Visx Star 2 excimer laser. One eye of each patient received a single drop of brimonidine tartrate 0.2% (brimonidine group) and the other eye, a single drop of a balanced salt solution (control group).

RESULTS: The study evaluated 136 eyes (68 patients). The difference in the incidence of subconjunctival hemorrhages was statistically significantly lower in the brimonidine group (mean score 2.24 ± 1.96 [SD]) than in the control group (mean score 7.61 ± 2.72) (*P*<.001). However, no eye in the control group and 7 eyes (10.4%) in the brimonidine group had a dislocated flap with folds on the first postoperative day (*P* .016). All eyes with dislocated flaps required surgical intervention. At 6 months, there was no significant difference between groups in the percentage of eyes achieving 20/20 or better uncorrected distance visual acuity, in the mean SE, or in the enhancement rate.

CONCLUSIONS: Brimonidine prevented the formation of subconjunctival hemorrhages after femtosecond LASIK but increased the risk for flap dislocation. Thus, surgeons are cautioned against the use of perioperative brimonidine to decrease hemorrhagic complications in femtosecond LASIK.

J Cataract Refract Surg 2009; 35:1338 1342 © 2009 ASCRS and ESCRS

The ultrashort-pulse femtosecond laser has been used successfully in several types of corneal procedures including the creation of corneal flaps in laser in situ keratomileusis (LASIK),[1] dissection of channels for intracorneal rings,[2] and preparation of donor and host tissue for keratoplasty.[3] As with any new technique, using the femtosecond laser for LASIK flap creation has advantages and disadvantages. A possible disadvantage of the femtosecond laser versus mechanical microkeratomes is that a longer period of suction is needed for the lamellar resection[4]; this may lead to an increased incidence of postoperative subconjunctival hemorrhages. Although from the surgeon's perspective subconjunctival hemorrhages may be considered a minor and temporary cosmetic problem, for a significant number of patients, the hemorrhages cause anxiety and false alarm in the immediate postoperative period.[5]

There have been attempts to decrease the incidence of subconjunctival hemorrhages through the use of drugs with vasoconstrictive effects, including brimonidine,[6,7] apraclonidine,[8,9] and phenylephrine.[10] However, there is controversial evidence that the use of perioperative vasoconstrictors may increase the incidence of flap complications caused by poor flap adherence. In a retrospective study, Walter and Gilbert[7] found a statistically significant increase in the incidence of a dislocated flap after LASIK with prophylactic brimonidine. However, another prospective study concluded that α_2-agonists applied topically decrease

0886 3350/09/$ see front matter
doi:10.1016/j.jcrs.2009.03.029

Eye Therapies Exhibit 2175, 1 of 5

Studies[6,7] have shown that the use of perioperative brimonidine can significantly decrease the incidence of bleeding complications after LASIK. However, there are contradictory results on whether prophylactic use of brimonidine increases the incidence of flap dislocation or slippage. In a retrospective noncompar-

6. Norden RA. Effect of prophylactic brimonidine on bleeding complications and flap adherence after laser in situ keratomileusis. J Refract Surg 2002; 18:468 471

Muñoz (EX-2175) at 1341–42.

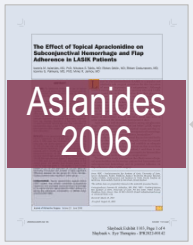
Reply (Paper 43) at 11 n.6; Sher Reply Decl. (EX-1049) ¶ 86.

Norden 2002 Discloses Actual Use of Brimonidine to Reduce Eye Redness in LASIK Patients

- Others in the field cited to Norden's finding that brimonidine reduced redness

> Norden[5] conducted a double-masked study and concluded that α-agonists applied topically may decrease hyperemia and subconjunctival hemorrhage after LASIK surgery significantly, without increasing the risk of flap slippage.

Aslanides 2005 (EX-1102) at 2239.e8.



> drugs,[5] topical apraclonidine applied just before LASIK surgery may cause vasoconstriction[5] of conjunctival vessels and thus reduce the occurrence and severity of subconjunctival hemorrhage, as described with another vasoconstrictor, brominidine.[6,7]

Aslanides 2006 (EX-1103) at 585, 588.

> a vasoconstrictive property. There are some reports that the preoperative use of topical brimonidine can help reduce bleeding-related problems during laser in situ keratomileusis (LASIK) and cataract surgery.[5,6] We deter-

Hong (EX-1104) at 469–70.

Reply (Paper 43) at 11; Sher Reply Decl. (EX-1049) ¶ 89.

Patent Owners Arguments All Fail

- Patent Owner's emphasis of "α1 effects" versus "α2 effects" is a red herring.
- A POSA would not have been motivated to use high concentrations of brimonidine to reduce eye redness
- Side effects of brimonidine would not have deterred a POSA from pursuing a low concentrations of brimonidine to reduce eye redness

Reply (Paper 43) at 10–17; Sher Reply Decl. (EX-1049) ¶¶ 63–97.

Patent Owner Is Incorrect that a POSAs Would Have Thought Brimonidine Would Cause Vasodilation

PATENT OWNER'S ARGUMENT:

> many prior commercial redness relievers contained α-1 agonists. By contrast, α-2 agonists (including brimonidine) were known to work by mediating vasodilation, congesting and engorging blood vessels, and making the eyes appear red or hyperemic—an "α-2 effect." Brimonidine, a highly selective α-2 agonist, had an

PO Resp. (Paper 30) at 4.

Reply (Paper 43) at 10–13; Sher Reply Decl. (EX-1049) ¶¶ 63–89.

Patent Owner's "α2 Effect" Argument in this Proceeding Is Inconsistent with the Intrinsic Evidence

NOECKER DECLARATION

"…brimonidine was known as a highly selective α2 agonist with ***vasodilation*** effects and plagued with undesirable side effects, including ocular redness and ocular allergic reactions, which exacerbate redness in patients."

* * *

"To the extent the concentration would have been expected to be in the range of brimonidine's α2 activity, the POSA would have expected brimonidine to cause ***vasodilation***, exacerbating redness rather than reducing redness in the eye."

* * *

"A highly selective α2 agonist having very little α1 vasoconstricting effect, brimonidine primarily caused ocular blood vessels to ***vasodilate*** and flood with blood, causing ocular hyperemia (i.e., eye redness)—the very property a POSA would have avoided when seeking to develop a redness reliever."

Noecker Decl. (EX-2020) ¶¶ 82, 216–20.

INTRINSIC EVIDENCE

category of a adrenergic receptor agonists. It is a known property of all a adrenergic receptor agonists, including brimonidine, to cause vasoconstriction. However, known formu-

'742 Patent (EX-1001) at 1:61–63.

"Further the alpha class of receptors has been further differentiated pharmacologically into alpha 1 and alpha 2 receptors, both of which have properties of vasoconstriction of vascular smooth muscle."

* * *

"Prior art views all alpha agonists, whether more alpha 1 selective, mixed, or more alpha 2 selective as having both desired vasoconstrictive properties and undesired ischemic consequences that are intrinsic to their use."

'481 Provisional (EX-1011) at 10.

Reply (Paper 43) at 12; Sher Reply Decl. (EX-1049) ¶¶ 63–65.

Patent Owner's "α2 Effect" Argument in this Proceeding Is Inconsistent with the Prior Art Evidence

Derick 1995 (EX-2169)

Burke 1996 (EX-1035)

Robin 1998 (EX-1018) at 32: "Locally in the eye, both brimonidine and apraclonidine produce **anterior segment (i.e., conjunctiva, iris, ciliary body) vasoconstriction**."

1990 | 2000 | 2010

Hong 2007 (EX-1104) at 470: ". . . [T]opical brimonidine administration before strabismus surgery reduced intraoperative bleeding and postoperative subconjunctival hemorrhage in adult patients, and is **as effective and as powerful as the well-known vasoconstrictor phenylephrine**."

Norden 2002 (EX-1006) at 468: "The alpha-2 adrenergic agonist drugs **as a class are also considered to be strong vasoconstrictors**."

Wikberg 2001 (EX-1017) at 2049: "The α2-adrenoceptor agonists brimonidine, apraclonidine, and oxymetazoline are **potent vasoconstrictors** in the porcine ciliary artery."

Dean (EX-1007) at 2:35-38: "Upon **topical ocular administration brimonidine causes vasoconstriction in scieral [scleral] vessels**. However, brimonidine does not appear to be a vasoconstrictor in the vessels in the back of the eye."

Reply (Paper 43) at 10–12; Sher Reply Decl. (EX-1049) ¶¶ 60–61, 68, 75–78, 79.

A POSA Would Have Been Motivated to Use Low Concentrations of Brimonidine to Reduce Eye Redness

GIL (EX-1004)

For ophthalmic application, preferably solutions are prepared typically containing from about 0.01% to about 0.5% of active ingredient, and a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should

following radial keratotomy surgery. One hundred and twenty-four male and female subjects, 21 to 45 years of age, undergo routine, elective, unilateral radial keratotomy for the correction of myopia and brimonidine is administered as a 0.03% ophthalmic solution.

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

Gil (EX-1004) at 3:63–66, 4:48–52, 5:31–34.

DEAN (EX-1007)

Brimonidine is a potent and relatively selective α_2 agonist which has been shown to effectively lower IOP in rabbits, monkeys and man. Upon topical ocular administration brimonidine causes vasoconstriction in scieral vessels. However, brimonidine does not appear to be a vasoconstrictor in vessels in the back of the eye. While brimonidine is a relatively safe compound it has been shown to cause the side effects of sedation and ocular hyperemia in an allergic like reaction in some patients. These side effects are thought to be due to the relatively high concentration of the drug administered topically. The sedation like side effects are believed to be caused by the drug crossing the blood brain barrier and triggering the sedative effects. The mechanism by which brimonidine causes hyperemia is not well understood. It is likely that the frequent instillation of relatively high drug concentrations causes this side effect. Thus, lowering the overall dose of brimonidine while maintaining IOP control would be advantageous.

Dean (EX-1007) at 2:33–50.

Petition (Paper 2) at 35–36, 58; Sher Decl. (EX-1002) ¶¶ 155–56; Reply (Paper 43) at 8,14; Sher Reply Decl. (EX-1049) ¶ 44.

Brimonidine Was Considered Safe and Comfortable

A 1-Year Study of Brimonidine Twice Daily in Glaucoma and Ocular Hypertension

A Controlled, Randomized, Multicenter Clinical Trial

Joel S. Schuman, MD; Barry Horwitz, MD; Neil T. Choplin, MD; Robert David, MD; Diane Albracht, MD; Kuankuan Chen, MS; and the Chronic Brimonidine Study Group

* * *

Conclusions: Brimonidine is safe and effective in lowering IOP in glaucomatous eyes. Brimonidine provides a sustained long-term ocular hypotensive effect, is well tolerated, and has a low rate of allergic response.

Schuman (EX-1022) at 847.

Brimonidine (Alphagan®): A clinical profile four years after launch

R. DAVID

Ophthalmology Clinical Research, Allergan, Irvine, CA - USA

* * *

All of the known brimonidine-associated side effects including ocular allergy and fatigue drowsiness are reversible and easily remedied. Moreover, all known side effects of brimonidine are generally minor and transient, and have little impact on patients' quality of life. However, the use of topical brimonidine should be avoided in newborns or young infants in which CNS depression has been reported (19, 20). This adverse

David (EX-1021) at S72, S76.

Petition (Paper 2) at 19; Sher Decl. (EX-1002) ¶¶ 35, 100; Laskar Decl. (EX-1003) ¶ 40.

Brimonidine's Side Effects Are Similar to the Side Effects of Other OTC Redness Reducers

DR. NOECKER

61. While these vasoconstrictors reduced redness, they have also triggered various side effects, including rebound hyperemia, tachyphylaxis, and medicamentosa. EX-1001 ('742 patent) at 2:11-13, 2:21-28; EX-1009 (Federal

Noecker Decl. (EX-2020) ¶ 61.

Acute and Chronic Conjunctivitis Due to Over-the-counter Ophthalmic Decongestants

Charles N. S. Soparkar, MD, PhD; Kirk R. Wilhelmus, MD; Douglas D. Koch, MD; Gary W. Wallace, MD; Dan B. Jones, MD

* * *

Results: Seventy patients (137 eyes) were identified. Preparations containing the vasoconstrictors naphazoline, tetrahydrozoline, or phenylephrine were associated with 3 clinical patterns of conjunctivitis: conjunctival hyperemia (50 cases), follicular conjunctivitis (17 cases), and eczematoid blepharoconjunctivitis (3 cases). Deconges-

* * *

Conclusion: Nonprescription decongestant eyedrops can produce acute and chronic forms of conjunctivitis by pharmacological, toxic, and allergic mechanisms. Once recognized, conjunctival inflammation often takes several weeks to resolve.

Soparkar (EX-1096) at 34–35.

Reply (Paper 43) at 10; Sher Reply Decl. (EX-1049) ¶ 91.

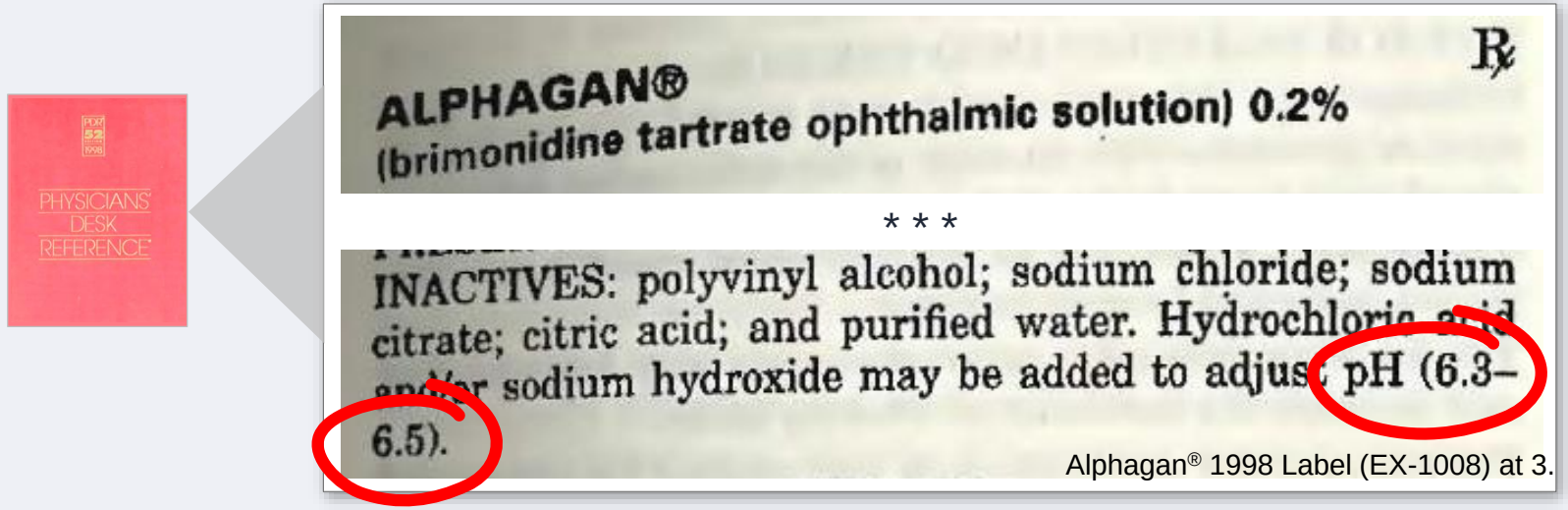
Claim 3 of the ’742 Patent Is Obvious

The ’742 Patent	Prior Art Ref.’s
[3.preamble] A method for reducing eye redness consisting essentially of	Gil (’553 patent) Norden 2002
[3.1] “topically administering”	Gil (’553 patent) Norden 2002
[3.2] “to a patient having an ocular condition”	Gil (’553 patent) Norden 2002
[3.3] “a composition consisting essentially of brimonidine”	Gil (’553 patent) Norden 2002
[3.4] “into ocular tissue”	Gil (’553 patent) Norden 2002
[3.5] “wherein pH of said composition is between about 5.5 and about 6.5”	Alphagan® Label
[3.6] “wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume”	Gil (’553 patent) Dean (’442 patent)*

*Express motivation to lower the concentration of brimonidine to reduce adverse events

Petition (Paper 2) at 50–56; Sher Decl. (EX-1002) ¶¶ 140–68; Gil (EX-1004); Norden (EX-1006); Dean (EX-1004).

Brimonidine Eye Drops with a pH of 6.3 to 6.5 Were Known



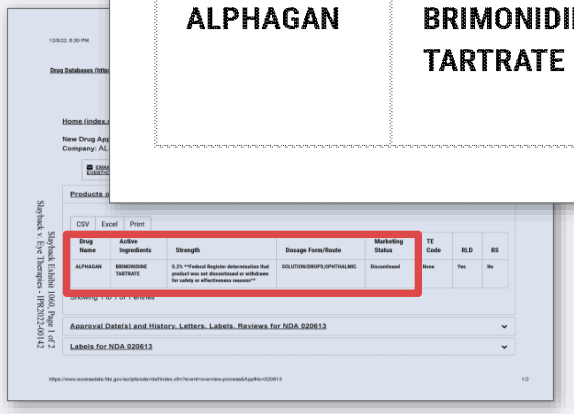
We therefore conclude that a prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness. That is not to say that the claimed composition having a narrower range is unpatentable. Rather, the existence of overlapping or encompassing ranges shifts the burden to the applicant to show that his invention would not have been obvious, as we discuss below.

In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003).

Reply (Paper 43) at 17, 20; Laskar Reply Decl. (EX-1048) ¶¶ 22–23, 26.

There Was No "Progression" Toward Higher pH Values

- Alphagan® 0.2% brimonidine was "safe and comfortable" and was discontinued for reasons other than safety or efficacy.



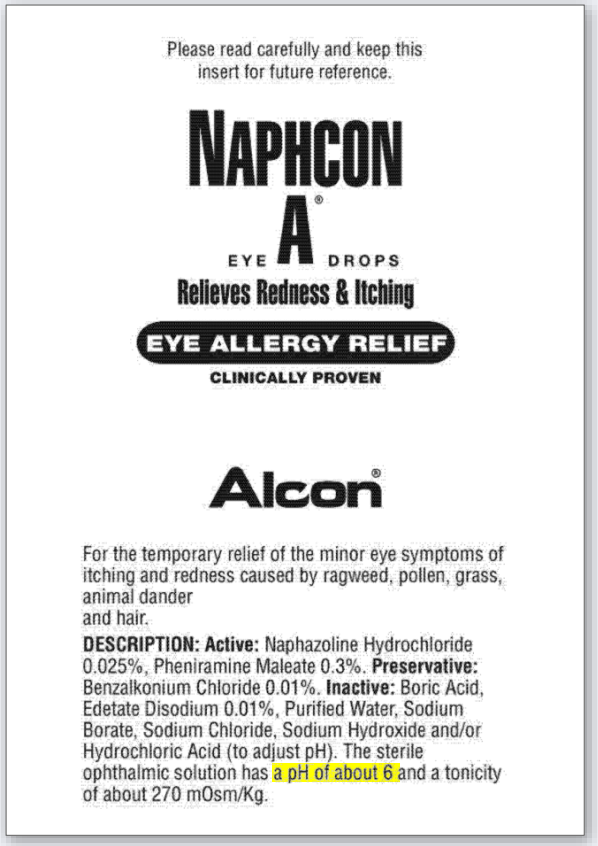
Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status
ALPHAGAN	BRIMONIDINE TARTRATE	0.2% **Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons**	SOLUTION/DROPS;OPHTHALMIC	Discontinued

Drugs@FDA (EX-1060) at 1.

Reply (Paper 43) at 18; Laskar Reply Decl. (EX-1048) ¶ 28;
Alphagan® P (0.1%, 0.15%) 2006 Label (EX-2014) at 1; Aieta (EX-1061) at 787; NDA-21770 (EX-1063) at 2.

A POSA Would Have Understood that Eye Drops Had pH Values in the Range of 5.5 to 6.5

- There is a wide range of pH that is well tolerated in patients.



Please read carefully and keep this insert for future reference.

NAPHCON A® EYE DROPS

Relieves Redness & Itching

EYE ALLERGY RELIEF

CLINICALLY PROVEN

Alcon®

For the temporary relief of the minor eye symptoms of itching and redness caused by ragweed, pollen, grass, animal dander and hair.

DESCRIPTION: Active: Naphazoline Hydrochloride 0.025%, Pheniramine Maleate 0.3%. **Preservative:** Benzalkonium Chloride 0.01%. **Inactive:** Boric Acid, Edetate Disodium 0.01%, Purified Water, Sodium Borate, Sodium Chloride, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH). The sterile ophthalmic solution has a pH of about 6 and a tonicity of about 270 mOsm/Kg.

Naphcon A (EX-1058).

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.5%

* * *

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.

ALPHAGAN®
(brimonidine tartrate ophthalmic solution) 0.2%

* * *

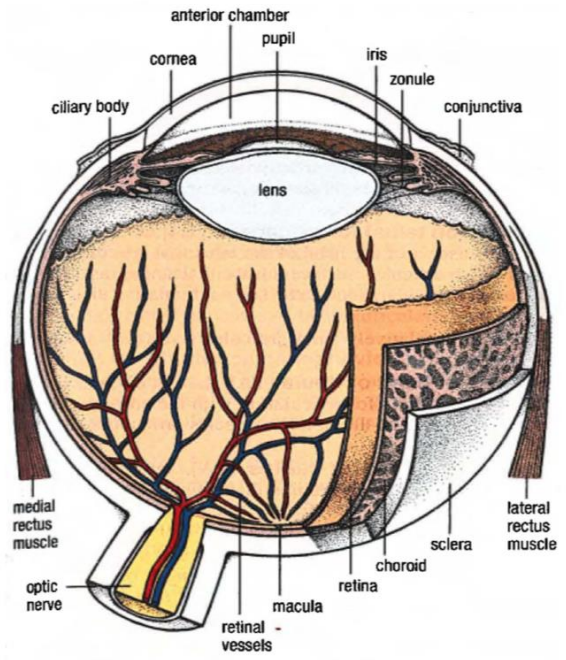
In solution, **ALPHAGAN®** (brimonidine tartrate ophthalmic solution) 0.2% has a clear, greenish-yellow color. It has an osmolality of 280 – 330 mOsml/kg and a pH of 5.6 - 6.6.

Each mL of **ALPHAGAN®** contains:
Active ingredient: brimonidine tartrate: 0.2% (2 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.

Alphagan® (0.5%, 0.2%) 2001 Label (EX- 2012) at 1, 6.

Reply (Paper 43) at 20–21; Laskar Reply Decl. (EX-1048) ¶¶ 19–25.

A POSA Would Have Been Motivated to Target Blood Vessels in the Conjunctiva



Stedman's 2006 (EX-1097) at 689.

A If we're talking about eye redness as relevant to this case, so we're talking about hyperemia mostly, predominantly, those are conjunctival blood vessels.

Q And they're not in the sclera?

A They are not in the sclera.

Q In relation to the sclera, where is the -- where are the conjunctival blood vessels?

A They're in the conjunctiva.

Q And where is that in relation to the sclera?

A It's superficial, in part, to the eye. It's superficial in the portion.

Q Okay. And superficial meaning it's on top of the episclera?

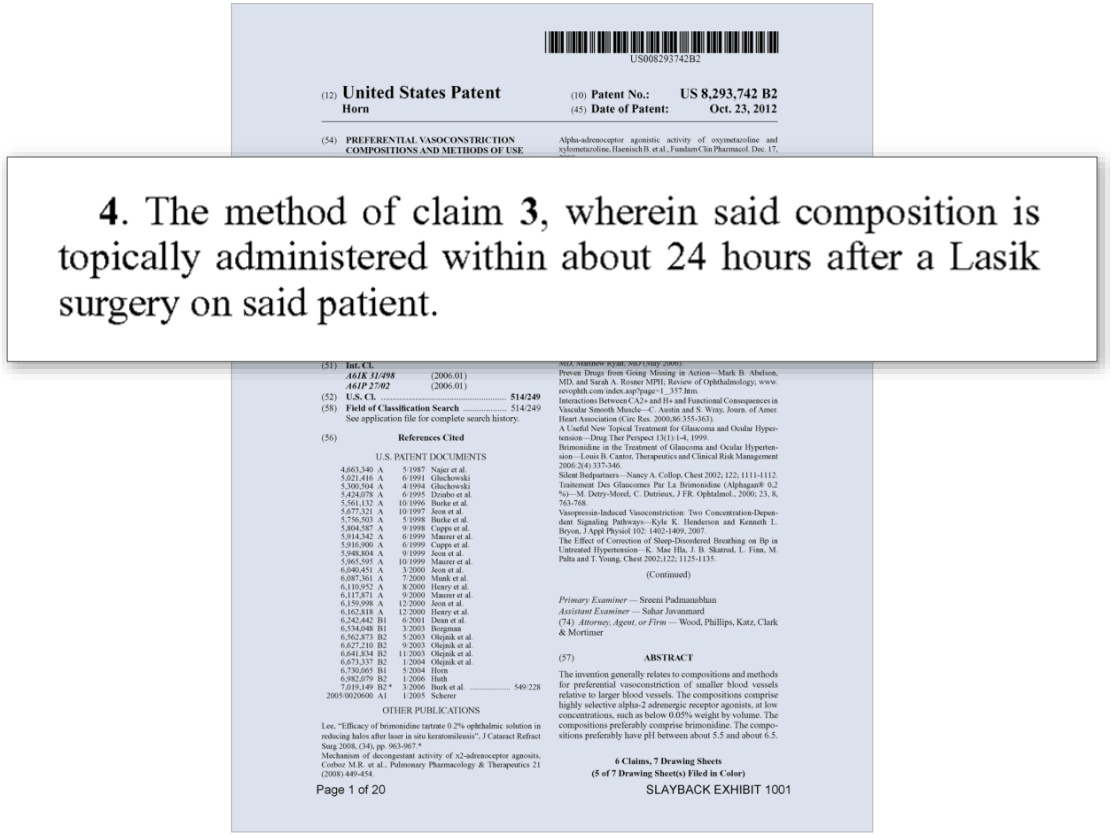
A Correct.

Noecker Dep. Tr. (EX-1053) at 19:16–20:21 (objection omitted).

Petition (Paper 2) at 55; Sher Decl. (EX-1002) ¶ 152; Reply (Paper 43) at 19–20; Sher Reply Decl. (EX-1049) ¶¶ 99–101, 104–105.

A POSA Would Expect Administration of Low Concentrations of Brimonidine to Reduce Redness *after* LASIK

- Norden discloses administration of brimonidine *prophylactically*, but a POSA would have known that administration pre- or post-operatively would reduce redness
- Gil (the ’553 patent) discloses administration of brimonidine *post-operatively* in radial keratotomy patients



US008293742B2

(12) **United States Patent**
Horn

(10) **Patent No.: US 8,293,742 B2**
(45) **Date of Patent: Oct. 23, 2012**

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

4. The method of claim **3**, wherein said composition is topically administered within about 24 hours after a Lasik surgery on said patient.

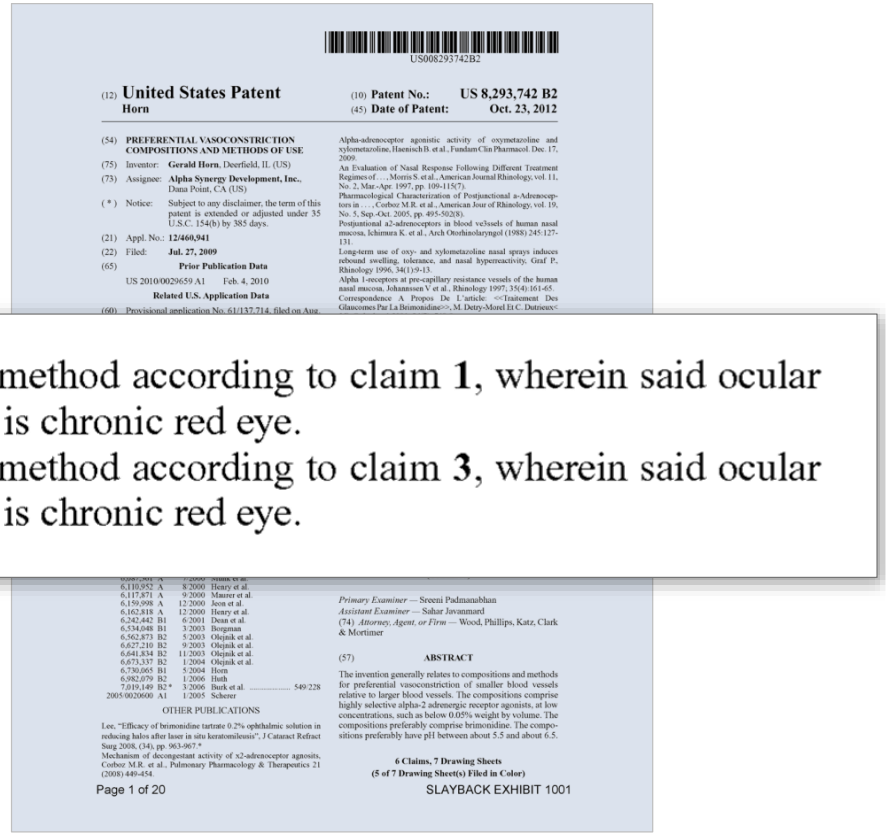
Page 1 of 20

SLAYBACK EXHIBIT 1001

Petition (Paper 2) at 61–62; Sher Decl. (EX-1002) ¶¶ 169–72; Reply (Paper 43) at 22; Sher Reply Decl. (EX-1048) ¶ 108.

There Is No Basis to Limit "Chronic Red Eye" to "Persistent and Constant Ocular Disorder"

- Specification does not provide a definition of "chronic red eye"
- One cause of chronic red eye would be seasonal allergies
- POSA would have expected brimonidine to reduce redness regardless of the underlying cause (e.g., hyperemia, hemorrhage, chronic red eye, etc.)



US008293742B2

(12) **United States Patent**
Horn

(10) **Patent No.: US 8,293,742 B2**
(45) **Date of Patent: Oct. 23, 2012**

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

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

(73) Assignee: **Alpha Synergy Development, Inc.**, Dana Point, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 385 days.

(21) Appl. No.: **12/460,941**

(22) Filed: **Jul. 27, 2009**

(65) **Prior Publication Data**

US 2010/0029659 A1 Feb. 4, 2010

Related U.S. Application Data

(60) Provisional application No. 61/137,714, filed on Aug.

5. The method according to claim **1**, wherein said ocular condition is chronic red eye.

6. The method according to claim **3**, wherein said ocular condition is chronic red eye.

Alpha-adrenoceptor agonistic activity of oxymetazoline and xylometazoline, Haenisch B. et al., Fundam Clin Pharmacol. Dec. 17, 2009.

An Evaluation of Nasal Response Following Different Treatment Regimes of . . . , Morris S. et al., American Journal Rhinology, vol. 11, No. 2, Mar.-Apr. 1997, pp. 109-115(7).

Pharmacological Characterization of Postjunctional a-Adrenoceptors in . . . , Corboz M.R. et al., American Jour of Rhinology, vol. 19, No. 5, Sep.-Oct. 2005, pp. 495-502(8).

Postjunctional a2-adrenoceptors in blood vessels of human nasal mucosa, Ichimura K. et al., Arch Otorhinolaryngol (1988) 245:127-131.

Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. Graf P, Rhinology 1996, 34(1):9-13.

Alpha 1-receptors at pre-capillary resistance vessels of the human nasal mucosa. Johanssen V et al., Rhinology 1997; 35(4):161-65.

Correspondence A. Propos De L'article: <<Traitement Des Glaucomes Par La Brimonidine>>, M. Detry-Morel Et C. Dutrieux<

6,110,952 A 8/2000 Henry et al.
6,117,871 A 9/2000 Maurer et al.
6,159,998 A 12/2000 Jeon et al.
6,162,818 A 12/2000 Henry et al.
6,242,442 B1 6/2001 Dean et al.
6,534,048 B1 3/2003 Borgman
6,562,873 B2 5/2003 Olejnik et al.
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6,982,079 B2 1/2006 Huth
7,019,149 B2 * 3/2006 Burk et al. 549/228
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Lee, "Efficacy of brimonidine tartrate 0.2% ophthalmic solution in reducing halos after laser in situ keratomileusis", J Cataract Refract Surg 2008, (34), pp. 963-967.*
Mechanism of decongestant activity of α2-adrenoceptor agnosits, Corboz M.R. et al., Pulmonary Pharmacology & Therapeutics 21 (2008) 449-454.

Primary Examiner — Sreeni Padmanabhan
Assistant Examiner — Sahar Javanmard
(74) *Attorney, Agent, or Firm* — Wood, Phillips, Katz, Clark & Mortimer

(57) **ABSTRACT**

The invention generally relates to compositions and methods for preferential vasoconstriction of smaller blood vessels relative to larger blood vessels. 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.

6 Claims, 7 Drawing Sheets
(5 of 7 Drawing Sheet(s) Filed in Color)

Page 1 of 20

SLAYBACK EXHIBIT 1001

Sher Decl. (EX-1002) ¶¶ 173–77; Reply (Paper 43) at 22; Sher Reply Decl. (EX-1048) ¶ 109.

Secondary Considerations Do Not Overcome a Strong Case of Obviousness

- The use of “low concentrations” of brimonidine was known in the prior art, e.g., Gil and Walters
- Commercially available redness relieving eye drops are not the closest prior art
- Patent Owner’s evidence of industry praise is unreliable
- Patent Owner fails to account for its award-winning marketing efforts of Lumify
- Patent Owner did not provide relevant information required to fully assess commercial success

> “Regardless of the secondary considerations that Patent Owner may assert, secondary considerations are insufficient to overcome a strong case of obviousness.”

Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Reply (Paper 43) at 22.

Patent Owner Admits that Its Objective Evidence Is "Directly Tied" to Features Known in the Art: Low-Concentration Brimonidine

The unexpected superiority of low-concentration brimonidine in reducing eye redness also led to a cascade of real-world benefits for users of Lumify, whose use in reducing eye redness is an embodiment of the claimed invention. EX-2020, ¶¶270-

* * *

Low-concentration brimonidine has multiple advantageous properties compared to the prior art ocular commercial vasoconstrictors, including its surprisingly superior redness reducing capability, its rapidity of onset and duration of action, and the lack of rebound hyperemia or tachyphylaxis. EX-2020, ¶303.

* * *

Moreover, its success is directly tied to the claimed invention: redness reduction using low-dose brimonidine. This is substantiated by Lumify's clear and

PO Resp. (Paper 30) at 66, 68.

"[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."

Ormco Corp. v. Align Tech., Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006).

Reply (Paper 43) at 22–23; PO Resp. (Paper 30) at 66, 68; Jarosz Decl. (EX-2024) ¶ 105.

Secondary Considerations:
Unexpected Results

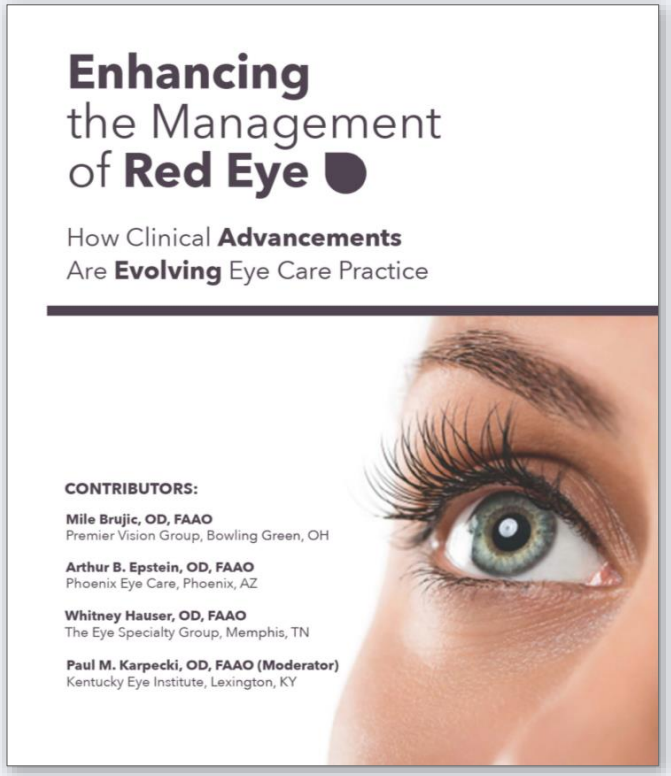
- Patent Owner's unexpected results is not probative of unexpected results because it does not compare to the closest prior art.
  - Patent Owner does not compare the method claimed in claims 3-6 to the '553 patent.

- Patent Owner's "unexpected results" is nothing more than an incremental improvement on the prior art, and does not override the strong evidence of obviousness
  - *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.,* 752 F.3d 967, 977 (Fed. Cir. 2014).

Reply (Paper 43) at 23–24.

Secondary Considerations:
Industry Praise

Patent Owner's industry praise is not tied to novel limitations but is based on its own advertisements and unsubstantiated website posts.



Enhancing the Management (EX-2199).

Bausch Article (EX-2165).

Lumify Science (EX-2163).

Reply (Paper 43) at 24–25; Jarosz Decl. (EX-1047) ¶¶ 18, 37–38.

Secondary Considerations: Commercial Success

- **Patent Owner claims that the commercial success of the product is attributable to "low concentration of brimonidine."**
  - Low concentrations of brimonidine are known in the prior art.
  - In other cases where the success of the product is primarily attributable to a single feature in the prior art, the Board and the Federal Circuit have found that this commercial success is not enough to overcome obviousness.
    - *See Ethicon Endo-Surgery, Inc. v. Covidien LP,* 812 F.3d 1023, 1034–35 (Fed. Cir. 2016).
- **Significant marketing expenses drove Lumify sales, which Patent Owner fails to account for.**
- **Patent Owner failed to provide relevant information necessary to assess commercial success.**

Reply (Paper 43) at 25–26.

Thank You

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) the undersigned hereby certifies that **"DEMONSTRATIVES OF PETITIONER SLAYBACK PHARMA LLC"** was served by email upon lead counsel for Patent Owner on February 20, 2023, with an updated version on February 22, 2023, pursuant to Patent Owner's agreement to accept service by email as set forth in Patent Owner's Mandatory Notices.

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Dated: February 22, 2023

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