EXHIBIT F

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT AND TRIAL APPEAL BOARD

FERRUM FERRO CAPITAL, LLC
Petitioner

v.

ALLERGAN SALES, LLC
Patent Owner

Patent No. 7,030,149

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,030,149

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TABLE OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 7,030,149 to Chang et al., titled "Combination of Brimonidine Timolol for Topical Ophthalmic Use" (the "'149 Patent")
1002	U.S. Patent No. 7,323,463 to Chang et al., titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use" (the "'463 Patent")
1003	U.S. Patent No. 7,320,976 to Chang et al., titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use" (the "'258 Patent")
1004	U.S. Patent No. 7,642,258 to Chang et al., titled "Combination of Brimonidine and Timolol for Topical Ophthalmic Use" (the "'258 Patent")
1005	Declaration of Anthony Palmieri, Ph.D.
1006	U.S. Patent No. 5,502,052 to DeSantis, titled "Use of a Combination of Apraclonidine and Timolol to Control Intraocular Pressure" ("DeSantis")
1007	Timmermans et al., "Structure-Activity Relationships in Clonidine-Like Imidazolidines and Related Compounds," pp. 21-60 in *Progress in Pharmacol.*, Vol. 3, No. 1 (1980) ("Timmermans")
1008	Larsson, "Aqueous Humor Flow in Normal Human Eyes Treated With Brimonidine and Timolol, Alone and in Combination," *Arch. Ophthalmol.*, April 2001, 119:492-495 ("Larsson")
1009	Stewart et al., "Comparison of the Efficacy and Safety of Latanoprost 0.005% Compared to Brimonidine 0.2% or Dorzolamide 2% When Added to a Topical β-Adrenergic Blocker in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension," *J. Ocular Pharmacol. Therapeutics*, 2000, 16:251-259 ("Stewart")

Exhibit No.	Description
1010	Clineschmidt et al., "A Randomized Trial in Patients Inadequately Controlled with Timolol Alone Comparing the Dorzolamide-Timolol Combination to Monotherapy with Timolol or Dorzolamide," *Opthalmology*, October 1998, 105:1952-1959 ("Clineschmidt")
1011	Airaksinen et al., "A Double-Masked Study of Timolol and Pilocarpine Combined," *Am. J. Ophthalmol.*, December 1987, 104:587-590 ("Airaksinen")
1012	*Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286 (Fed. Cir. 2013)
1013	Web page at JAMA Opthalmology (publisher of former Archives of Ophthalmology) for April 2001 issue of *Archives of Ophthalmology*, Volume 119
1014	Front and date-stamped (April 11, 2001) pages of *Archives of Ophthalmology*, Volume 119, retrieved from hardcopy of journal issue at New York Academy of Medicine Library
1015	Shin et al., "Long-term Brimonidine Therapy in Glaucoma Patients With Apraclonidine Allergy," *Am. J. Ophthalmol.*, May 1999, 127:511-515 ("Shin")
1016	Hutzelmann et al., "Comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol and the concomitant administration of dorzolamide and timolol: a clinical equivalence study," *Br. J. Ophthalmol.*, 1998, 82:1249-1253 ("Hutzelmann")
1017	Zadok et al., "Combined Timolol and Pilocarpine vs Pilocarpine Alone and Timolol Alone in the Treatment of Glaucoma," *Am. J. Ophthalmol.*, June 1994, 117:728-731 ("Zadok")
1018	Curriculum vitae of Anthony Palmieri, Ph.D.

I. INTRODUCTION

Ferrum Ferro Capital, LLC ("FFC," or "Petitioner") requests *inter partes* review of claim 4 of U.S. Patent No. 7,030,149 (the "'149 Patent"), assigned to Allergan Sales LLC ("Patent Owner"), and cancellation of the claim as unpatentable under 35 U.S.C. § 103(a).

FFC is a privately-held venture focused upon innovation, the strategic deployment of capital towards socially beneficial ends, and related investment strategies. FFC's diligent investigation regarding Patent Owner's patenting tactics and Hatch-Waxman litigation surrounding its tellingly named "Combigan®" glaucoma drug have led to this petition to cancel claim 4 of the '149 Patent, which is being asserted by the Patent Owner to prevent generic manufacturers from offering lower-cost treatment solutions to glaucoma victims.

The '149 Patent is a member of a family of patents, also including U.S. Patent No. 7,323,463 (the "'463 Patent"), generally directed to a combination formulation of prior art active ingredients brimonidine and timolol for treatment of glaucoma. Glaucoma treatments such as brimonidine and timolol are applied topically to the eye multiple times a day, and patients usually require more than one drug for effective treatment. Patients apply the drugs serially if they are not available in combination formulations, but patients can inadvertently miss doses as the quantity of drugs and daily administrations increase. Patient compliance with

the resulting complicated dosage regimens has therefore been a significant issue, and simplifying dosage regimens to enhance patient compliance has been a motivation in the field pointing towards combination formulations for glaucoma.

In litigation involving the Combigan® patents, the Federal Circuit addressed the combination formulation of the prior art active ingredients timolol and brimonidine, and invalidated the composition claims in the related '463 Patent. In doing so, the Federal Circuit underscored the compelling case for obviousness here: The two active ingredients were available individually for glaucoma treatment prior to the Combigan® patents, the motivation to combine them into a single formulation was provided expressly in the prior art, and there was a reasonable expectation of success because the prior art taught that these classes of active ingredients were complementary and should be combined to benefit the patient.

The Federal Circuit also addressed the corresponding method claim 4 of the '149 Patent, but split in a 2-1 decision in which the majority interpreted the claim more narrowly than the dissent and found it not invalid. However, when interpreted under the broadest reasonable interpretation standard applicable in *inter partes* review proceedings, claim 4 would have been obvious for the same reasons as the composition claims of the '463 Patent. Claim 4 of the '149 Patent should therefore be cancelled as obvious over the prior art as set forth in this petition.

Because of its particular relevance to the challenged claim, this petition includes a summary of the Federal Circuit's prior art and obviousness analysis in its overview of the '149 Patent. The petition then addresses claim construction, technology background, and detailed bases of the obviousness ground with respect to claim 4 of the '149 Patent.

II. STANDING AND PROCEDURAL STATEMENTS

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the '149 Patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review of the '149 Patent. Petitioner files this petition in accordance with 37 C.F.R. § 42.106(a), and files concurrently with this petition a Power of Attorney and an Exhibit List pursuant to 37 C.F.R. §§ 10(b) and 42.63(e), respectively. The required fee is paid via online credit card payment.

III. MANDATORY NOTICES

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

The real parties-in-interest are FFC and Deep Lake Holdings, LLC. FFC is a Delaware company which is majority owned and controlled by Deep Lake Holdings, LLC, also a Delaware company. Kevin Barnes is the sole beneficial owner of, and has all of the voting interest in, Deep Lake Holdings, LLC. No other entity or person has authority to direct or control Petitioner's actions or decisions relating to this petition. FFC is funding all of the fees and costs of this petition for *inter partes* review.

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

On information and belief, the following judicial and administrative matters would affect, or be affected by, a decision in this proceeding.

1. *Allergan, Inc. v. Sandoz Inc.*, Case No. 2:09-cv-00097 (E.D. Tex.)

2. *Allergan, Inc. v. High-Tech Pharmacal Co.*, Case No. 2:09-cv-00182 (E.D. Tex.) (consolidated with 2:09-cv-00348)

3. *Allergan, Inc. v. Alcon Laboratories, Inc. et al.*, Case No. 2:09-cv-00348 (E.D. Tex.)

4. *Allergan, Inc. v. Apotex Inc. et al.*, Case No. 2:10-cv-00200 (E.D. Tex.)

5. *Allergan, Inc. v. Watson Laboratories, Inc. et al.*, 2:10-cv-00344 (E.D. Tex.)

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	**Back-Up Counsel**
Amir Naini, Ph.D. Reg. No. 45,770 Russ August & Kabat 12424 Wilshire Blvd., 12th Fl. Los Angeles, CA 90024 Phone: (310) 826-7474 Fax: (310) 826-6991 anaini@raklaw.com	Jeffrey Liao Reg. No. 63,037 Russ August & Kabat 12424 Wilshire Blvd., 12th Fl. Los Angeles, CA 90024 Phone: (310) 826-7474 Fax: (310) 826-6991 jliao@raklaw.com

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

Petitioner consents to service by e-mail at the addresses of counsel provided above.

IV. STATEMENT OF PRECISE RELIEF REQUESTED

Pursuant to 37 C.F.R. § 42.22(a), Petitioner states that claim 4 of the '149 Patent is unpatentable under 35 U.S.C. § 103(a) as obvious over DeSantis (Ex. 1006) in view of Timmermans (Ex. 1007) and further in view of Larsson (Ex. 1008) and/or Stewart (Ex. 1009). Petitioner seeks cancellation of claim 4. Petitioner's full statement of the reasons for the relief requested is set forth in detail in Section IX below.

V. OVERVIEW OF THE '149 PATENT

A. Background

The '149 Patent (Ex. 1001) issued on April 18, 2006, from application Ser. No. 10/126,790, filed April 19, 2002. The '149 Patent is a member of a family of patents generally directed to a composition of 0.2% brimonidine and 0.5% timolol and methods of using the composition. The patents relate to Allergan's Combigan®, a combination eye-drop product for treating glaucoma. The patent family includes the '463 Patent" (Ex. 1002), and U.S. Patent Nos. 7,320,976 (the "'976 Patent," Ex. 1003) and 7,642,258 (the "'258 Patent," Ex. 1004).

Both brimonidine and timolol are prior art active ingredients used to treat glaucoma long before the earliest priority date of the Combigan® patent family.

As discussed in more detail below, the Federal Circuit has invalidated claims to the combination of these prior art active ingredients in the '463 Patent for obviousness. Over a dissenting opinion that fundamentally resulted from differing views on claim interpretation, two judges of the Federal Circuit panel held method claim 4 of the '149 Patent not invalid despite the invalidity of the corresponding composition claims of the '463 Patent. However, for the reasons set forth in this petition, the method of claim 4 is invalid under the standards applicable in *inter partes* review and should be canceled as obvious.

B. Claim Language

Claim 4 of the '149 Patent provides:

> 4. A method of reducing the number of daily topical ophthalmic doses of brimonidine administered topically to an eye of a person in need thereof for the treatment of glaucoma or ocular hypertension from 3 to 2 times a day without loss of efficacy, wherein the concentration of brimonidine is 0.2% by weight, said method comprising administering said 0.2% brimonidine by weight and 0.5% timolol by weight in a single composition.

Claim 1 of the '463 Patent is exemplary of the other patents in the family. It provides:

> 1. A composition comprising about 0.2% brimonidine by weight and about 0.5% timolol by weight as the sole active agents, in a single composition.

C. Federal Circuit Decision

1. Related '463 Patent

In *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286 (Fed. Cir. 2013), the Federal Circuit invalidated the claims of the '463 Patent for obviousness. (Ex. 1012.) In reaching its decision, the court noted that "both timolol and brimonidine were commercially available drugs used for ophthalmic conditions at the time of the invention." *Id.* at 1291. In fact, "they were available in their claimed concentrations …." *Id.* Furthermore, "it was known that the serial administration of brimonidine and timolol reduced intraocular pressure [in glaucoma] greater than either timolol or brimonidine alone." *Id.* The primary prior art reference, DeSantis, "expressly provided a motivation to formulate fixed combinations of alpha2-agonists [the class of drugs in which brimonidine fell] and beta blockers, including timolol, in order to increase patient compliance." *Id.* The court also noted evidence that the prior art taught serial administration of the two active ingredients, dosing of the individual active ingredients twice a day when used serially, numerous other fixed combination products in the field for treatment of ocular hypertension and glaucoma, and known advantages to using fixed combinations including twice daily dosing as opposed to three times a day. *Id.* at 1290.

Against this "strong case" for obviousness, the court then measured the arguments relied upon by the Patent Owner, and found them lacking. First, because the Patent Owner argued that patient compliance was not a motivation because it was not a factor the FDA considered in approving Combigan®, the court considered whether it was necessary for motivation to combine in drug patent obviousness analysis for the claimed invention to be directed to a factor for FDA approval. The court explained that, while FDA approval may be considered if, for example, it went to motivation to develop a drug or skepticism regarding drug efficacy, "[t]here is no requirement in patent law that the person of ordinary skill be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval. Motivation to combine may be found in many places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications." *Id.* at 1291-92.

The court then pointed to multiple sources for motivation to develop the claimed combination drug product. DeSantis taught the fixed combination of a beta-blocker such as timolol with an alpha2-agonist such as brimonidine. *Id.* at 1292. Other references taught fixed combinations of other ophthalmic drugs, and numerous other fixed combination products for treatment of ocular hypertension and glaucoma were on the market at the time of the invention. *Id.* In addition, it was common at the time of the invention to administer brimonidine and timolol

serially, and DeSantis taught increasing patient compliance through fixed-combination formulations. *Id.*

Second, the Federal Circuit addressed reasonable expectation of success. The court acknowledged that "formulation science carries with it a degree of unpredictability," but emphasized that "'obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'" *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007)). "DeSantis showed that alpha2-agonists and beta blockers are complementary and should be used together." *Id.* With respect to the Patent Owner's difficulties with preservatives during development of particular formulations related to Combigan®, the court explained that there is no requirement for a person of ordinary skill to have a reasonable expectation of success in developing Combigan®, but only a reasonable expectation of success in developing the claimed invention. *Id.* Importantly, even for claims reciting a particular preservative called "BAK," the Patent Owner's unsuccessful efforts to develop a formulation with a different preservative were not probative of expectation of success with respect to BAK. *Id.* Moreover, Petitioner notes that claim 4 of the '149 Patent does not recite BAK, any other preservative, or any other ingredient other than brimonidine and timolol, and DeSantis taught that those two classes of active ingredients are complementary and combinable.

Third, with respect to certain aspects of the art that the Patent Owner argued taught away, such as potential side effects, different dosage regimens, and disparate half lives of brimonidine and timolol, the Federal Circuit found that, as a whole, the art did not teach away because of the clear motivation to combine expressed in DeSantis. *Id.* at 1293.

Fourth, the Federal Circuit addressed secondary considerations. As for the district court's findings regarding long-felt need, the Federal Circuit dismissed this factor because the district court's findings were conclusory and an unexplained need for combination products that Combigan® met at some level could not be found to outweigh the strong case of obviousness. *Id.*

With respect to unexpected results, the Federal Circuit noted that prior attempts to treat patients twice per day with brominidine resulted in some loss of efficacy eight to nine hours after administration (which was referred to as the "afternoon trough"), and that the combination formulation did not suffer from this loss of efficacy. *Id.* However, even accepting this unexpected result with respect to loss of efficacy, the Federal Circuit found that it could not outweigh the "extensive evidence in the prior art showing the concomitant administration of brimonidine, and timolol multiple times per day, that the combination had benefits over the administration of either alone, and that there was a motivation to combine the two to achieve better patient compliance." *Id.* (citing *KSR Int'l Co. v. Teleflex*

Inc., 550 U.S. 398, 426 (2007)). The court concluded that "[w]hether or not that combination also solved problems associated with the afternoon trough, we find the motivation to make the combination was real." *Id.*

2. '149 Patent

When considering the obviousness of claim 4 of the '149 Patent, two judges of the Federal Circuit panel found that "[c]laim 4 is similar to the claims of the '463 patent with the exception that it contains the additional limitation that the daily number of doses of brimonidine be reduced from 3 to 2 times a day *without loss of efficacy*." *Id.* at 1293-94 (emphasis in original). Based on its interpretation of claim 4 as reciting an additional limitation of no loss of efficacy, the majority found the claim not invalid over the prior art. *Id.* at 1294.[1]

The dissenting judge pointed out that "the method of claim 4 consists of a single step: applying a fixed combination of 0.2% brimonidine and 0.5% timolol

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[1] The majority also construed the unrelated phrase "administered in separate compositions" in claims 1-3 of the '149 Patent, and the dissenting judge agreed with the majority's construction of that term. *Id.* at 1295. Construction of "administered in separate compositions" in claims 1-3 is irrelevant to the question of whether recitation of "without loss of efficacy" in claim 4 is a claim limitation or not—an issue on which the Federal Circuit majority and dissent disagreed.

twice a day." *Id.* at 1296. He recognized, and disagreed with, the majority's view that the claim recited no loss of efficacy as a claim requirement. *Id.* "Avoiding a 'loss of efficacy' is not a separate step, but rather a result of the claimed method." *Id.* Based on his broader interpretation, the dissenting judge would have invalidated claim 4 as obvious, because "the different results as between the claims of the '463 patent and claim 4 of the '149 patent cannot be reconciled." *Id.* at 1295. The single step of applying a fixed combination of the two prior art active ingredients twice a day was "surely obvious to try." *Id.* (citing *KSR*, 550 U.S. at 421).

To be sure, the majority and dissenting opinions discussed the issue of whether claim 4 would have been obvious in terms of whether no loss of efficacy was an inherent property of using the claimed combination, and discussion of the "without loss of efficacy" term was included in the court's consideration of invalidity rather than a separate claim construction section. The majority noted however that Sandoz, the patent challenger, did not argue or present evidence on inherency, so analysis of whether or not avoiding the loss of efficacy was inherently disclosed was inconclusive. *Id.* at 1294. As a result, the disagreement among the judges over whether claim 4 of the '149 Patent was obvious flowed from the differing opinions regarding whether or not "without loss of efficacy" was a claim limitation or step—if so, the majority stated that it differentiated claim 4

from the invalidated claims of the '463 Patent, and if not, the dissent stated that claim 4 was obvious for the same reasons as the claims of the '463 Patent.[2]

VI. LEVEL OF ORDINARY SKILL IN THE ART

The level of ordinary skill in the art may be ascertained from the '149 Patent and the relevant prior art. The relevant field is pharmaceutical formulation and applications of such formulations for ophthalmic uses.

Petitioner submits the Declaration of Anthony Palmieri, Ph.D., Associate Scholar of Pharmaceutics at the University of Florida College of Pharmacy. Dr. Palmieri has substantial education and experience in pharmaceutical formulation dating from his Ph.D. in pharmaceutics from the University of Georgia and his early academic career as Associate Professor of Pharmaceutics at the University of Wyoming, through his industrial experience at Pharmacia and The Upjohn Company (which also included substantial experience in patent evaluation), and his current academic position at the University of Florida College of Pharmacy. His current teaching responsibilities, which include practical laboratory sessions in

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[2] Because the majority found claim 4 of the '149 Patent not invalid and the generic pharmaceutical companies would not be able to enter the market based on that claim, the court found it unnecessary to address the claims of the '258 and '976 Patents. *Allergan*, 726 F.3d at 1294 n.2.

addition to classroom teaching, cover topics including dose form design, biopharmaceutics and pharmacokinetics for ophthalmic pharmaceutical dosage forms.

Dr. Palmieri states that a "person of ordinary skill in pharmaceutical formulation and applications of such formulations for ophthalmic uses as of April 19, 2002, earliest possible priority date of the '149 Patent would have been had a Ph.D. in pharmaceutics, pharmaceutical chemistry, pharmacology or related field, or an M.D. with significant background in pharmaceutics, pharmaceutical chemistry, pharmacology or related field, and with a background in the development of pharmaceutical formulations for ophthalmic treatments. This person would have had experience, through his or her background in development of pharmaceutical formulations, in evaluating how dosage forms would impact patient treatment." (Ex. 1005, ¶ 13.)

VII. CLAIM CONSTRUCTION

A. Broadest Reasonable Interpretation Standard

Pursuant to 37 C.F.R. § 42.100(b), the challenged claim is given its broadest reasonable interpretation in light of the specification of the '149 Patent. The Federal Circuit recently confirmed that the broadest reasonable interpretation standard is the correct one to apply in *inter partes* review proceedings for an unexpired patent. *In re Cuozzo Speed Techs., LLC*, No. 2014-1301, 2015 U.S.

App. LEXIS 1699, *13-*24 (Fed. Cir. Feb. 4, 2015). In contrast to the broadest reasonable interpretation, courts apply the principles of claim construction as set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) to interpret claims in litigation.

B. "Without Loss of Efficacy" Is Not a Claim Limitation Under the Broadest Reasonable Interpretation

In the Federal Circuit decision concerning claim 4 of the '149 Patent, the majority and dissenting judges had differing interpretations of the "without loss of efficacy" claim language. The majority considered it a claim limitation; the dissent did not. The broadest reasonable interpretation is therefore that "without loss of efficacy" is not a claim limitation because that interpretation is the broader of the two set forth in the Federal Circuit's analysis under the narrower *Phillips* standard.

It is reasonable to interpret claim 4 such that "without loss of efficacy" is not a limitation. Dr. Palmieri attests that a person of ordinary skill in the art would have understood "without loss of efficacy" in claim 4 as an intended result and not a step of the claimed process. (Ex. 1005, ¶ 21-22.) The method of claim 4 has a single step of applying a fixed combination of 0.2% brimonidine and 0.5% timolol twice a day. There is no separate step in the claimed method with respect to the "without loss of efficacy" language. Rather, that language recites the intended result of practicing the method and should therefore not be given weight. *See Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1380-81 (Fed.

Cir. 2003) (finding that claim term "traded efficiently" should "not [be] given weight when it simply expresses the intended result of a process step positively recited"); MPEP § 2111.04.

VIII. COMBINATION DRUGS FOR TREATMENT OF GLAUCOMA

The '149 Patent is generally directed to combination drug treatments for glaucoma. This section provides background regarding glaucoma and intraocular pressure, as well as the alpha-2 agonist and beta-blocker classes of drugs used since at least the mid-1990s to treat glaucoma. The section also provides background regarding the state of the art regarding dosage regimens, acceptable glaucoma drugs, and recognition of the advantages associated with fixed combinations for glaucoma treatment.

A. Glaucoma and Intraocular Pressure

Glaucoma is an eye disorder that is typically characterized by elevation in intraocular pressure, also called intraocular hypertension. (*See* Palmieri Decl., Ex. 1005, ¶¶ 23-42.) If left untreated, the elevated intraocular pressure can result in optic nerve damage and loss of vision. Glaucoma and its characteristic elevation of intraocular pressure are thought to be caused by overproduction of fluid (aqueous humor) in the eye or inadequate outflow of fluid from the eye. Glaucoma and intraocular hypertension have therefore long been treated using drug therapies that decrease intraocular pressure.

B. Drug Therapies for Glaucoma

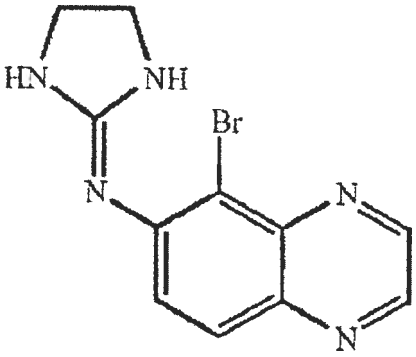
1. Alpha-2 Agonists and Beta-Blockers

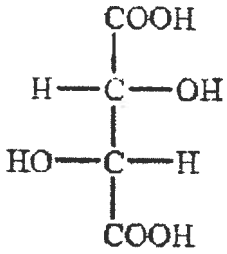
By the mid-1990s, classes of drugs used to treat glaucoma and intraocular hypertension included alpha-2 agonists and beta-blockers. For example, DeSantis discusses the various classes of drugs used at that time for glaucoma treatment, including alpha-2 agonists and beta-blockers, and goes on to describe his invention specifically as the combination of alpha-2 agonists and beta-blockers in a single composition. (Ex. 1006 at 1:14-2:23; Ex. 1005 at ¶ 25.)

Alpha-2 agonists activate alpha-2 adrenergic receptors and are thought to reduce aqueous humor production and increase outflow, and beta-blockers are adrenergic receptor blocking agents that are thought to reduce aqueous humor production and possibly also increase outflow. (Ex. 1005 at ¶ 26.)

As the '149 Patent acknowledges, brimonidine is an alpha-2 agonist that "is disclosed in U.S. Patent No. 3,890,319. The use of brimonidine for providing neuroprotection to the eye is disclosed in U.S. Patent Nos. 5,856,329; 6,194,415; and 6,248,741." (Ex. 1001 at 1:29-32.) Brimonidine was therefore known long before the '149 Patent as an alpha-2 agonist for ophthalmic uses. (Ex. 1005 at ¶ 27.)

Brimonidine's chemical formula (including an L-tartrate component) is:

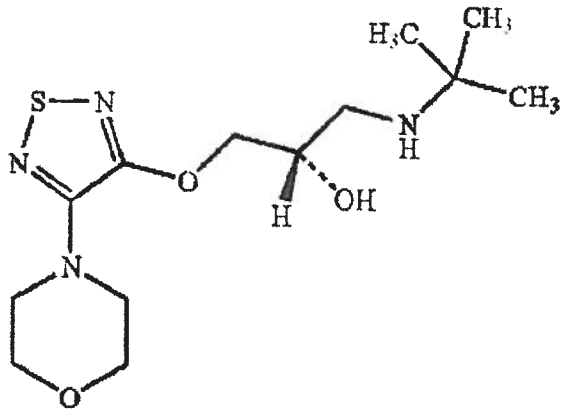




(Ex. 1001 at 1:40-50.)

Similarly, the '149 Patent acknowledges that timolol is a beta-blocker that, "as an ophthalmic drug, is disclosed in U.S. Patent No. 4,195,085 and 4,861,760." (*Id.* at at 1:33-34.) Timolol was therefore also known long before the '149 Patent. (Ex. 1005 at ¶ 29.)

Timolol's chemical formula is:



(Ex.1001 at 1:55-67.)

2. Combination of Brimonidine and Timolol for Glaucoma

As DeSantis explains, "[a] significant number of glaucoma patients are required to administer more than one drug in order to achieve therapeutic control of their intraocular pressure." (Ex. 1006 at 1:42-44.) DeSantis notes that then-existing treatment regimens for glaucoma often required administration of two or more drugs in separate doses several times per day. (*Id.* at 2:1-5.) DeSantis then points out that "[p]atient compliance with such complicated dosage regimens can be very poor, particularly in elderly patients. Since the majority of glaucoma patients are elderly, this patient compliance problem is significant." (*Id.* at 2:6-9.; *see also* Ex. 1005, ¶ 31.)

DeSantis expressly teaches that fixed combinations of alpha-2 agonists and beta-blockers can enhance patient compliance. (*Id.* at 2:10-23.) DeSantis discloses use of the beta-blocker timolol in fixed combinations. (*Id.* at 2:34; 5:21-32.) Indeed, timolol is the only beta-blocker claimed in DeSantis. (*Id.* at 6:42-48.) DeSantis also discloses the use of alpha-2 agonists that it terms "clonidine-like drugs," and references the disclosure of Timmermans. (*Id.* at 4:42-50.) Timmermans discloses brimonidine. (Ex. 1007 at 28, Fig. 31.; *see* Ex. 1005 at ¶¶ 32-34.)

3. State of the Art Regarding Dosage Regimens and Acceptable Alpha-2 Agonists and Beta-Blockers

Before the earliest claimed priority date of the '149 Patent, the art taught the serial administration of 0.2% brimonidine with 0.5% timolol. (Ex. 1005, ¶¶ 35-37.) Specifically, Larsson reported dosage regimens involving twice-daily topical administrations of 0.2% brimonidine alone, 0.5% timolol alone, and serial administration of 0.2% brimonidine followed by 0.5% timolol after a five minute period. (Ex. 1008 at 493, "Subjects and Methods.")

In addition, other publications in the art taught dosing the serial applications of brimonidine and timolol twice per day. Stewart reported a retrospective analysis of glaucoma patient records in which brimonidine, among other alpha-2 agonists, was used with beta-blockers including timolol. Significantly, in the patient records reviewed and reported by Stewart, "[n]o difference statistically was observed in the three-month intraocular pressure between twice and three times daily dosing for brimonidine [when combined with a beta-blocker]...." (Ex. 1009 at 253, "Results.") This disclosure taught a person of ordinary skill in the art that brimonidine and timolol could be dosed twice daily when used in combination. (Ex. 1005, ¶ 37.)

Before the '149 Patent, there were three pharmaceutically acceptable alpha-2 agonists for treating glaucoma and ocular hypertension: clonidine, apraclonidine, and brimonidine. (Ex. 1005, ¶ 38.) Of these three alpha-2 agonists, brimonidine

was favored because it did not suffer from the ocular allergy that apraclonidine caused at a high rate, and it generally had fewer side effects than the other alpha-2 agonists. (*Id.*)

4. State of the Art Regarding Fixed Combination Drug Treatments

Before the '149 Patent, fixed combination treatments for glaucoma and ocular hypertension were common in the field. Fixed combinations such as dorzolamide/timolol (Cosopt®) and pilocarpine/timolol (Timpilo®) were in use. (Ex. 1005, ¶ 39 (citing Exs. 1016 and 1017).) Also, prior to these fixed combinations, the active ingredients were used individually in monotherapies or serial applications of the individual active ingredients. (*Id.*)

Combining active ingredients addressed problems of patient compliance with complicated dosing schedules. As the authors of one article in the field put it, "the administration of two different eyedrops, one twice a day and the other four times a day, may have a significant adverse effect on patient compliance, which is a common problem in glaucoma therapy. … Combining these two drugs into a single solution appears to be the logical approach." (Ex. 1017 at 728.).

In addition, the art taught other advantages associated with fixed combinations for glaucoma treatment. (Ex. 1005, ¶¶ 41-42.) For example, Clineschmidt compared timolol monotherapy dosed twice a day and dorzolamide monotherapy dosed three times a day to a fixed combination of dorzolamide and

timolol dosed twice a day, and found the fixed combination to be more effective than monotherapy with either agent alone. (Ex. 1010 at 1952.) In another example, Airaksinen showed that a fixed combination of pilocarpine and timolol given twice a day was as effective as pilocarpine monotherapy given four times a day, and superior to pilocarpine given two times a day. (Ex. 1011 at 587, 590.)

IX. DETAILED EXPLANATION OF OBVIOUSNESS GROUND

Claim 4 of the '149 Patent is unpatentable under 35 U.S.C. § 103(a) as obvious over DeSantis (Ex. 1006) in view of Timmermans (Ex. 1007), and further in view of Larsson (Ex. 1008) and/or Stewart (Ex. 1009). The obviousness ground is supported by the declaration of Dr. Palmieri. (Ex. 1005.)

A. Availability of References as Prior Art

The '149 Patent claims priority to an application filed April 19, 2002. DeSantis, Timmermans, and Stewart were all issued or published more than one year prior to this earliest priority date of the '149 Patent, and are therefore prior art under 35 U.S.C. § 102(b).

Larsson indicates on its face that it was published in the "APR 2001" issue (Vol. 119) of Archives of Ophthalmology. The web page at JAMA Ophthalmology, the present publisher of the former Archives of Ophthalmology, concerning the relevant issue of the journal indicates a publication date of April 1, 2001. (Ex. 1013.) In addition, a copy of the April 2001 issue of Archives of

Ophthalmology retrieved from the New York Academy of Medicine is date-stamped April 11, 2001. (Ex. 1014.) On these bases, Larsson is prior art under 35 U.S.C. § 102(b). At a minimum, Larsson is prior art under § 102(a). Patent Owner may in theory seek to challenge Larsson's status as § 102(a) art and swear behind Larsson, though Petitioner notes that Larsson was considered as available prior art in the prior litigation and Petitioner does not expect that Patent Owner will seek to challenge Larsson's status as prior art in this proceeding. However, at least for this reason of potential swearing behind, Petitioner submits that Stewart and Larsson are not redundant of one another and should both be considered and included in institution of the requested *inter partes* review. In addition, Petitioner reserves its rights with respect to establishing that Larsson is available as prior art under 35 U.S.C. § 102(b)

B. It Would Have Been Obvious to Make a Fixed Combination of Brimonidine and Timolol

Claim 4 is a method with the single step of administering a fixed combination of 0.5% brimonidine and 0.2% timolol twice per day. It would have been obvious to a person of skill in the art to combine 0.5% brimonidine and 0.2% timolol in a fixed combination for twice daily use in glaucoma treatment.

The Federal Circuit already determined that the fixed combination of 0.5% brimonidine and 0.2% timolol for glaucoma treatment would have been obvious

when it invalidated the composition claims of the related '463 Patent. The Federal Circuit's reasoning applies equally to method claim 4 of the '149 Patent.

DeSantis teaches the use of alpha-2 agonists and beta-blockers in fixed combinations for treatment of glaucoma. (Ex. 1006 at 2:34; 5:21-32; 6:42-48.; Ex. 1005, ¶ 44.) DeSantis discloses the beta-blocker timolol, and references Timmermans for alpha-2 agonists. (*Id.* at 4:42-50.; Ex. 1005, ¶ 44.) Timmermans discloses brimonidine. (Ex. 1007 at 28, Fig. 31.; Ex. 1005, ¶ 44.)

Additional teachings in the art would have made it obvious to a person of ordinary skill to combine timolol and brimonidine. Larsson teaches serial administration of 0.2% brimonidine followed by 0.5% timolol after a five minute period. (Ex. 1008 at 493, "Subjects and Methods"; Ex. 1005, ¶ 45.) Stewart also teaches serial administration of brimonidine and timolol. (Ex. 1009 at 253, "Results"; Ex. 1005, ¶ 45.)

To the extent that the Patent Owner argues (despite what the Federal Circuit's called a "strong case" of obviousness for the fixed combination) that a person of skill would not have been motivated to combine brimonidine in particular with timolol, the art teaches otherwise. Before the '149 Patent, there were three pharmaceutically acceptable alpha-2 agonists: clonidine, apraclonidine, and brimonidine. (Ex. 1005, ¶ 38.) Of these three, brimonidine was favored for long-term treatment (as required for glaucoma) because apraclonidine had a high

rate of ocular allergy whereas brimonidine did not, and brimonidine had fewer side effects than the alternatives. (*Id.*) A person of ordinary skill in the art therefore would have been aware of multiple indicia in the field pointing to selection of brimonidine as the alpha-2 agonist in the fixed combination.

C. It Would Have Been Obvious to Dose the Fixed Combination Twice Daily

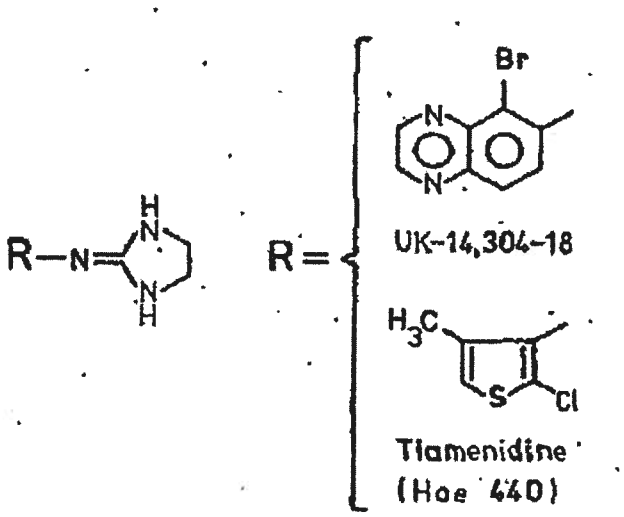
It would have been obvious to a person of ordinary skill to dose the fixed combination of brimonidine and timolol twice daily for glaucoma treatment. Larsson teaches twice daily serial administration of brimonidine and timolol. (Ex. 1008 at 493, "Subjects and Methods"; Ex. 1005, ¶ 47.) Stewart teaches twice daily serial administration, as well as no difference in intraocular pressure effects of the twice daily dosing when compared to three times a day dosing. (Ex. 1009 at 253, "Results"; Ex. 1005, ¶ 47.) Furthermore, DeSantis expressly provides motivation to combine the active ingredients into a fixed combination to increase patient compliance through a simpler dosage regimen. (Ex. 1006 at 2:1-22; Ex. 1005, ¶ 48.) Just as the motivation of patient compliance expressed in DeSantis would have led a person of skill to the fixed combination in the first place, it would have also motivated the use of a twice daily dosage regimen rather than a harder-to-follow regimen of three daily doses. (Ex. 1005, ¶ 48.)

The chart below provides further detail and exemplary quotations from the prior art in support of the obviousness ground for claim 4.

D. Claim Chart Showing Exemplary Citations from DeSantis (Ex. 1006) in View of Timmermans (Ex. 1007), and Further in View of Larsson (Ex. 1008) and/or Stewart (Ex. 1009)

US Patent 7,030,149	Exemplary Prior Art Disclosures
Claim 4	
4. A method of reducing the number of daily topical ophthalmic doses of brimonidine administered topically to an eye of a person in need thereof for the treatment of glaucoma or ocular hypertension from 3 to 2 times a day without loss of efficacy,	**DeSantis:** "[A] therapy regimen which includes use of two or more pharmaceutical compositions … requires the patient to apply the compositions to the affected eyes in separate, spaced dosages, several times per day. Patient compliance with such complicated dosage regimens can be very poor particularly in elderly patients. Since the majority of glaucoma patients are elderly, this patient compliance problem is significant. "In light of the foregoing circumstances, it is clear that a need exists for new, more potent antiglaucoma compositions which … enhance patient compliance. … "The present invention is directed to the provision of antiglaucoma compositions which comprise a combination of one or more alpha-2 agonists and one or more beta-blockers. The invention is also directed to methods of controlling intraocular pressure utilizing those compositions." (Ex. 1006 at 2:1-22.) **Larsson:** "The subjects reported to the test area at 8 AM on the day before aqueous humor flow was measured. They were given approximately 20 μL of 0.2% brimonidine in one eye and approximately 20 μL of placebo in the other eye. The procedure was repeated at 5 PM. The next day, when aqueous humor flow was measured, eyedrops were reinstilled at 8 AM. In part 2, brimonidine and placebo eyedrops were administered according to the same schedule as in part 1, but on every point for eyedrop instillation, approximately 20 μL of 0.5% timolol was also administered to both eyes 5 minutes after the other eyedrops, i.e., timolol was also

	administered twice daily." (Ex. 1008 at 493, "Subjects and Methods.") **Stewart:** "In this current study, we retrospectively evaluated the efficacy and safety of latanoprost 0.005% once daily, brimonidine 0.2% twice daily or dorzolamide 2% twice daily added to a topical β-blocker over three months of chronic therapy." (Ex. 1009 at 252, "Introduction.") "All topical β-blockers were allowed in this study to simulate usual clinical practice." (*Id.* at "Materials and Methods.") "No difference statistically was observed in the three-month intraocular pressure between twice and three times daily dosing for brimonidine (P = 0.45) or dorzolamide (P = 0.28), so the results from the two dosing schedules were combined for this report." (*Id.* at 253, "Results.")
wherein the concentration of brimonidine is 0.2% by weight,	**DeSantis:** "The alpha-2 agonists which can be employed in the compositions of the present invention include all pharmaceutically acceptable compounds which have alpha-2 agonist activity and are effective in controlling intraocular pressure." (Ex. 1006 at 3:17-21.) *See* Palmieri Decl. (Ex. 1005) at ¶ 38 **DeSantis:** "[A]lpha-2 agonists which may be utilized in the present invention include … 'clonidine-like' drugs. A comprehensive discussion of the properties of clonidine and clonidine-like compounds is presented in a publication by Timmermans et al. titled 'Structure-Activity Relationships in Clonidine-Like Imidazolidines and Related Compounds' …." (Ex. 1006 at 4:34-46.)

	Timmermans:  (Ex. 1007 at 28, Fig. 31.) UK-14,304-18 is brimonidine. **Larsson:** "The subjects … were given approximately 20 µL of 0.2% brimonidine …." (Ex. 1008 at 493, "Subjects and Methods.") **Stewart:** "In this current study, we retrospectively evaluated the efficacy and safety of … brimonidine 0.2% twice daily … added to a topical β-blocker over three months of chronic therapy." (Ex. 1009 at 252, "Introduction.")
said method comprising administering said 0.2% brimonidine by weight and 0.5% timolol by weight in a single composition.	**DeSantis:** "Beta-blockers, such as timolol … are also known to lower intraocular pressure …." (Ex. 1006 at 2:34.) "Specific examples of beta blockers which may find use in the present invention include … timolol …." (*Id.* at 5:21-32.) "What is claimed is: 1. A method of controlling intraocular pressure which comprises applying to the affected eye a therapeutically effective amount of a composition comprising: … 0.01 to 3.0 wt. % of timolol …." (*Id.* at 6:41-46.)

	Larsson: "[B]rimonidine and placebo eyedrops were administered … but on every point for eyedrop instillation, approximately 20 μL of 0.5% timolol was also administered to both eyes 5 minutes after the other eyedrops, i.e., timolol was also administered twice daily." Larsson (Ex. 1008 at 493, "Subjects and Methods.")

E. Secondary Considerations Do Not Overcome the Obviousness Ground

The Patent Owner raised two secondary considerations in the litigation that do not overcome the obviousness of claim 4 here.

First, the Federal Circuit found the secondary consideration of long-felt need to be so conclusory and without support that it rejected it even for the composition claims at issue. *Allergan*, 726 F.3d at 1293. Any argument based on long-felt need for the method of claim 4 is similarly unavailing.

Second, the Federal Circuit majority addressed the unexpected result of no loss of efficacy with twice daily dosing and found that it did not outweigh the extensive evidence in the art that a person of skill would have been motivated to combine the active ingredients in a fixed combination to achieve better patient compliance. *Id.* With respect to the method of claim 4, any argument that Patent Owner may make that the unexpected result renders the single-step method non-obvious should be rejected under the broadest reasonable interpretation of the claim. Simply put, "without loss of efficacy" is not a claim limitation that the

Patent Owner can rely upon to argue non-obviousness over the prior art, but is simply the intended result of the obvious process step of the claim. As such, the language is not given weight and an unexpected result tied to "without loss of efficacy" is not a relevant secondary consideration.

X. CONCLUSION

For all of the foregoing reasons, Petitioner respectfully requests *inter partes* review of claim 4 of the '149 Patent, and cancellation of the claim.

Respectfully submitted,

Date: March 9, 2015

/ Amir Naini /

RUSS AUGUST & KABAT
12424 Wilshire Blvd., 12th Fl.
Los Angeles, CA 90025
(310) 826-7474

Amir Naini
Reg. No. 45,770
Attorney for Petitioner
Ferrum Ferro Capital, LLC

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the above captioned **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 7,030,149** and copies of Exhibit Nos. 1001 to 1018 were served via FedEx on March 9, 2015 at the official correspondence address for the attorney of record for U.S. Patent No. 7,030,149 as shown in the USPTO PAIR system:

Allergan, Inc.
Attn: Legal Department
2525 DuPont Drive, T2-7H
Irvine, CA 92612-1599

Date: March 9, 2015

/ Amir Naini /

RUSS AUGUST & KABAT
12424 Wilshire Blvd., 12th Fl.
Los Angeles, CA 90025
(310) 826-7474

Amir Naini
Reg. No. 45,770
Attorney for Petitioner
Ferrum Ferro Capital, LLC

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT AND TRIAL APPEAL BOARD

FERRUM FERRO CAPITAL, LLC
Petitioner

v.

ALLERGAN SALES, LLC
Patent Owner

Patent No. 7,030,149

FERRUM FERRO CAPITAL, LLC'S
POWER OF ATTORNEY

Pursuant to 37 C.F.R. § 42.10(b), Petitioner Ferrum Ferro Capital, LLC, a Delaware limited liability company, hereby appoints the following practitioners as its attorneys to transact all business in the United States Patent & Trademark Office associated with the above-captioned *inter partes* review of U.S. Patent No. 7,030,149:

Lead Counsel	**Back-Up Counsel**
Amir Naini Reg. No. 45,770 Russ August & Kabat 12424 Wilshire Blvd., 12th Fl. Los Angeles, CA 90025 Phone: (310) 826-7474 Fax: (310) 826-6991 anaini@raklaw.com	Jeffrey Liao Reg. No. 63,037 Russ August & Kabat 12424 Wilshire Blvd., 12th Fl. Los Angeles, CA 90025 Phone: (310) 826-7474 Fax: (310) 826-6991 jliao@raklaw.com

For Ferrum Ferro Capital, LLC

Signature: Kevin Barnes

By: Kevin Barnes

Title: Principal

Date: 3/9/2015

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the above captioned **FERRUM FERRO CAPITAL, LLC'S POWER OF ATTORNEY** was served via FedEx on March 9, 2015 at the official correspondence address for the attorney of record for U.S. Patent No. 7,030,149 as shown in the USPTO PAIR system:

Allergan, Inc.
Attn: Legal Department
2525 DuPont Drive, T2-7H
Irvine, CA 92612-1599

Date: March 9, 2015

/ Amir Naini /

RUSS AUGUST & KABAT
12424 Wilshire Blvd., 12th Fl.
Los Angeles, CA 90025
(310) 826-7474

Amir Naini
Reg. No. 45,770
Attorney for Petitioner
Ferrum Ferro Capital, LLC