

Paper No. \_\_\_\_\_

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ARGENTUM PHARMACEUTICALS LLC

Petitioner,

v.

ALLERGAN, INC.,

Patent Owner.

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U.S. Patent No. 8,629,111

*Inter Partes* Review No. IPR2016-01232

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**PETITION FOR INTER PARTES REVIEW OF  
U.S. PATENT NO. 8,629,111**

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## I. INTRODUCTION

Argentum Pharmaceuticals LLC (“Petitioner”) requests review of U.S. Patent No. 8,629,111 to Acheampong *et al.* (“the ’111 patent,” EX1001) that issued on January 14, 2014. PTO records indicate the ’111 patent is assigned to Allergan, Inc. (“Patent Owner”). This Petition demonstrates a reasonable likelihood that claims 1-27 of the ’111 patent are unpatentable in view of the identified prior art.

The ’111 patent claims a topical ophthalmic emulsion as in related U.S. Patent No. 8,685,930 but further recites that cyclosporin A (“CsA”) is the only peptide present in the emulsion. Each element of the emulsion, including the claimed CsA and castor oil percentages, preferred ratios for combining them, and CsA as the only peptide present in the emulsion, was disclosed in a single prior art reference (Ding ’979) for use in topical ophthalmic emulsions to treat the same dry eye disease, such as keratoconjunctivitis sicca (“KCS”). In fact, during prosecution of a parent application, applicants admitted that the claimed emulsion containing 0.05% CsA and 1.25% castor oil “is squarely within the teaching of the Ding [’979] reference” and “would have been obvious” to a person of skill in the art at the time of the invention. EX1005, 0435; EX1002, ¶18.

Four years later, in prosecuting the ’111 patent as a continuation application, applicants changed course and attempted to withdraw these admissions. EX1004,

0007. They argued that data collected *after* their earlier admissions established patentability because of an alleged unexpected result that the emulsion was “equally or more therapeutically effective for the treatment of dry eye/keratoconjunctivitis sicca than the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil.” EX1004, 0007, 0205; EX1002, ¶¶20-22. The supposed “unexpected results” are weak, at best, and fail to rebut the strong evidence of obviousness. The data relied upon by applicants lack scientific parameters necessary to demonstrate statistical significance and materiality and, in many cases, appear to be copies of graphs from a § 102(b) prior art reference, Sall. Thus, Patent Owner’s cited evidence does not support non-obviousness of the claims, and merely confirms that the results were expected in view of and were already disclosed in the prior art.

#### **A. Overview of the ’111 Patent**

The ’111 patent has an earliest claimed priority date of September 15, 2003. Independent claim 1 recites an emulsion of 0.05% CsA in 1.25% castor oil, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer (“cross-polymer”) and water, wherein CsA is the only peptide present in the emulsion. Claims 2-6 and 9-10 recite that the emulsion comprises a tonicity or demulcent agent, specifically glycerine, and/or a buffer, specifically sodium hydroxide. Claim 12 specifies a range of pH values for the emulsion of claim 6, which comprises

glycerine and a buffer. Dependent claims 7-8 specify known weight percentages of polysorbate 80 and cross-polymer, respectively. Claim 11 recites that, when the emulsion is administered to the eye, there is substantially no detectable concentration of CsA in the blood.

Independent claim 13 recites an emulsion incorporating the ingredients and/or weight percentage limitations of claims 1 and 7-9, and the pH value recited in claim 12. Dependent claims 14-17 specify that the buffer is sodium hydroxide, the tonicity component is glycerine, the blood has substantially no detectable concentration of CsA, and that the emulsion is effective in treating KCS.

Independent claim 18 recites the same emulsion as claim 13 but specifies glycerine as the tonicity/demulcent agent and sodium hydroxide as buffer.

Dependent claim 19 recites the same pH range as claims 1 and 13.

Claims 20-22 depend from claim 1, claims 23-24 depend from claim 13, and claims 25-27 depend from claim 18. Claims 20, 23, and 25, claims 21 and 26, and claims 22, 24, and 27, respectively recite that the emulsion is therapeutically effective in treating dry eye disease or KCS, or in increasing tear production.

## **B. Overview of the Prosecution History**

U.S. Patent Application No. 13/967,163 (“the ’163 application”) was filed on August 14, 2013, and issued five months later on January 14, 2014, as the ’111 patent. The ’163 application is a continuation, via U.S. applications 13/961,828

and 11/897,177, of U.S. application 10/927,857 (“the ’857 application,” EX1005), which claims the benefit of U.S. provisional application 60/503,137, filed September 15, 2003.

During prosecution of the related ’857 application, Patent Owner admitted that Composition II, which is identical to the emulsion claimed in the ’111 patent, EX1002, ¶¶18-19, was “squarely within the teachings of Ding [’979]”:

***[A]pplicants concede that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at Composition II of the present application. The differences are insignificant.... As the examiner correctly observes, one of ordinary skill in the art “would readily envisage” such a composition, especially in view of Example 1B: having selected 0.05% as the concentration of cyclosporin, Example 1B (wherein the ratio of cyclosporin to castor oil is 0.04) teaches that the concentration of castor oil should be 1.250% (0.05%/1.250% = 0.04). The applicants concede that in making this selection (0.05% cyclosporin and 1.250% castor oil) there would have been a reasonable expectation of success; the differences between Examples 1A-1E and Composition II are too small to believe otherwise. The formulation of Composition II is squarely within the teachings of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise[.]***

EX1005, 0435 (emphases added).

During prosecution of the ’163 application, applicants acknowledged their prior admissions but claimed that newly-collected evidence supported the



patentability of the claims “[s]ince these comments have been filed.” EX1004, 0007. The examiner subsequently rejected the claims as obvious over Ding ’979. *Id.* at 0170-89. Patent Owner responded to the rejection, arguing that “the *prima facie* case of obviousness has not been properly established against the pending claims” and that the claims were patentable based on objective indicia. *Id.* at 0235. A terminal disclaimer was filed for the applications or parent applications that resulted in the ’930, ’556, ’162, ’048, and ’191 patents. *Id.* at 0159-60.

In remarks accompanying a Notice of Allowance, *id.* at 0428, EX1002, ¶23, the examiner concluded that applicants had failed to demonstrate commercial success or long-felt need. EX1004, 0439-41. Relying on declarations submitted by Drs. Schiffman and Attar, the examiner stated that “the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or [KCS]” and, therefore, “demonstrate[s] surprising and unexpected results.” *Id.* at 0443.

The alleged “unexpected results” are addressed in the declaration of Dr. Dileep Bhagwat accompanying this Petition. EX1002, ¶¶122-46. As Dr. Bhagwat notes, applicants’ data lacks scientific parameters necessary to demonstrate statistical significance and materiality. In many cases, the data appear to be repackaged from graphs published in the prior art. Sall reference asserted against

the claims in this Petition. Thus, applicants' declarations do not demonstrate surprising or unexpected results. *Id.*

During prosecution, the Patent Owner did not identify, and the examiner did not address, deficiencies in the Schiffman and Attar Declarations that made them unreliable, which are discussed in this Petition. Considering the new information presented herein and supported by Dr. Bhagwat's testimony, the Board ought not defer to the examiner's conclusions which relied on the one-sided information.

In addition to demonstrating the flaws in Patent Owner's alleged unexpected results, Dr. Bhagwat's declaration provides insight not previously presented to the Patent Office about how a person of ordinary skill in the art would interpret Ding '979. Among other things, Dr. Bhagwat's testimony establishes that the presently claimed emulsion would have been immediately apparent to one of ordinary skill in the art based on Ding '979. EX1002, ¶¶97-98, 114. The Patent Owner's alleged evidence of unexpected results cannot render patentable an anticipated claim. *In re Wiggins*, 488 F.2d 538, 543 (C.C.P.A. 1973).

Further, this Petition presents new arguments based on expert testimony as to why the claims are obvious over Ding '979 and other references that were not substantively analyzed during prosecution. Among other things, Dr. Bhagwat explains that the 1.25% castor oil emulsion vehicle of Example 2C in Ding '979 was the only vehicle that was most preferred for both the 0.05% and 0.10% CsA

emulsions, and that Sall's 0.05% and 0.10% CsA emulsions used the same castor oil vehicle. Petitioner provides an even stronger *prima facie* obviousness case than the examiner considered during prosecution. Accordingly, the Board should institute review without deference to the limited analysis during prosecution.

### **C. Overview of the Scope and Content of the Prior Art**

A prior art reference anticipates a claim if it discloses all elements of the claimed combination, or if the claimed combination would be "immediately apparent to one of ordinary skill in the art," or "at once envisaged" from the prior art reference. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012). An obviousness analysis requires an evaluation of any differences between the claimed subject matter and the asserted prior art. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). The obviousness inquiry may consider inferences that would be employed by a person of ordinary skill in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

1. U.S. Patent No. 5,474,979 to Ding *et al.* ("Ding '979," EX1006)

Ding '979 issued on December 12, 1995, and is prior art under 35 U.S.C. § 102(b). EX1006. Ding '979 teaches topical ophthalmic emulsions for the treatment of KCS or "dry eye disease/KCS." *Id.* at 5:9-12; EX1002, ¶61. Claims 7-8 recite emulsions containing 0.05-0.40% CsA in 0.625-5.00% castor oil, 1.00% polysorbate 80, 0.05% Pemulen<sup>®</sup> (an acrylate/C10-30 alkyl acrylate cross-

polymer), 2.20% glycerine, sodium hydroxide, and water, and having a pH range of 7.2-7.6. EX1006, 4:4-5; *id.* at 6:27-42; EX1002, ¶64. Ding '979 teaches that CsA is effective in treating dry eye disease/KCS “as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.” EX1006, 1:10-16, 37-39.

Ding '979 discloses four examples of castor oil-based vehicles (Examples 2A-D) for delivery of CsA. EX1006, 4:44-54; EX1002, ¶65. Example 2C is the exact same castor oil vehicle used in the challenged claims. Ding '979 discloses CsA-containing emulsions in Example 1 using the vehicles from Example 2. EX1006, 4:32-54. Example 1's emulsions have CsA and castor oil percentages covering the ranges disclosed in claims 7 and 8 (0.05%–0.40% CsA and 0.625%–5.00% castor oil) of Ding '979. *Id.* at 4:32-43; EX1002, ¶¶66, 70. One emulsion (Example 1D) specifically used the 1.25% castor oil vehicle (Example 2C) to deliver 0.10% CsA. EX1006, 4:32-43.

Ding '979 identifies a “more preferred” range for the ratio of CsA to castor oil of 0.02-0.12. *Id.* at 3:17-20; EX1002, ¶67. Each exemplified CsA-containing emulsion in Ding '979 falls within a narrower ratio range of 0.04-0.08, which, for the 1.25% castor oil vehicle (Example 2C) disclosed in Ding '979, equates to a CsA range of 0.05% to 0.10% CsA. EX1006, 4:32-43; EX1005, 0435; EX1002, ¶¶67, 94. Ding '979 does not expressly discuss twice-daily administration of the emulsions.

2. Sall *et al.*, *Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease*, 107 *Ophthalmology* 631 (2000) (EX1007)

Sall is prior art under 35 U.S.C. § 102(b). Sall describes a multi-center, randomized, double-masked Phase 3 clinical trial that assesses the safety and efficacy of increasing tear production and treating dry eye disease/KCS by twice-daily ophthalmic administration of 0.05% or 0.10% CsA in a castor oil emulsion, compared to the emulsion vehicle without CsA in the same regimen. EX1007, 631-32 & n.1; *id.* at figs. 1-4; EX1002, ¶¶73-74. Sall teaches the 0.05% CsA emulsion was safe and effective, was at least as effective as the 0.10% CsA emulsion, and resulted in fewer adverse side effects and in trough CsA blood concentrations below 0.1 ng/mL. EX1007, 631, 634-37; EX1002, ¶¶73-77, 80. Sall does not expressly disclose the exact composition of the vehicle, but compares the 0.05% and 0.10% CsA emulsions to the same vehicle. EX1007, 632; EX1002, ¶¶111-12.

3. A. Acheampong *et al.*, *Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, in Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2: Basic Science and Clinical Relevance* 1001 (eds. David A. Sullivan & Darlene A. Dartt 1998) (“Acheampong”) (EX1008)

Acheampong is prior art under 35 U.S.C. § 102(b). Acheampong describes administration of CsA formulations having from 0.05%-0.4% twice-a-day to

human patients with KCS for three months. EX1008, 1002; EX1002, ¶¶85-86.

Acheampong measured CsA blood concentration at both peak and trough levels following topical ophthalmic administration. EX1008, 1002. No detectable amount of CsA was measured in patients receiving the 0.05% CsA emulsion. EX1008, 1002, 1004; EX1002, ¶¶85-86.

**D. Overview of the Level of Skill in the Art**

A person of ordinary skill in the relevant field as of September 15, 2003 would likely have some combination of: (a) experience formulating pharmaceutical products; (b) experience designing and preparing drug emulsions intended for topical ocular administration; and (c) the ability to understand results and findings presented or published by others in the field. EX1002, ¶36. Typically this person would have an advanced degree, such as a medical degree, or a Ph.D. in organic chemistry, pharmaceutical chemistry, medicinal chemistry, pharmaceuticals, physical pharmacy, or a related field, or less education but considerable professional experience in these fields. *Id.* at ¶35.

Petitioner's expert, Dr. Dileep Bhagwat, is a Senior Pharmaceutical Consultant and the CEO of WPDC, LLC which focuses on consulting on pharmaceutical (formulation) development, quality, clinical and global regulatory filings. In this capacity, Dr. Bhagwat has consulted for U.S. and foreign companies. EX1002, ¶1; EX1003. Dr. Bhagwat received an M.S. and Ph.D. in

Industrial Pharmacy from St. John's University, New York. He also received an MBA in International Business from Pace University, New York, and a B.S. in Pharmacy from Bombay University, India.

Dr. Bhagwat has worked in the pharmaceutical industry for over 35 years. His work encompasses pharmaceutical research and development and pharmaceutical quality, manufacturing, regulations. He has worked on many dosage forms, for example solid/liquid oral (immediate released/controlled release), sub-lingual, intra-nasal, topicals (patches/creams/lotions/gels/emulsions), injectables, and metered dose inhalers. Dr. Bhagwat has been responsible for all aspects of drug product development (Phase I – III).

Dr. Bhagwat is an inventor on 16 U.S. issued patents plus numerous international patents. He has lectured and presented at various pharmaceutical and medical conferences including at the American Association of Pharmaceutical Scientists (AAPS), American Pain Society (APS), European Hematology Association, American Society of Hematology (ASH), and the Controlled Release Society.

Dr. Bhagwat is well qualified as an expert, possessing the necessary scientific, technical, and other specialized knowledge and training to assist in an understanding of the evidence presented herein, as well as possessing the expertise

necessary to determine and explain the level of ordinary skill in the art as of September 2003. EX1003.

## **II. GROUNDS FOR STANDING**

Petitioner certifies that, under 37 C.F.R. § 42.104(a), the '111 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review of the '111 patent on the grounds identified.

## **III. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8**

Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1)): The following real parties-in-interest are identified: KVK-TECH, Inc.; Argentum Pharmaceuticals LLC; Intelligent Pharma Research LLC; APS GP LLC; and APS GP Investors LLC.

Related Matters (37 C.F.R. § 42.8(b)(2)): An IPR petition for the '111 patent was filed by Apotex Corp. and Apotex Inc. as IPR2015-01282, as were petitions for related U.S. Patent Nos. 8,648,048 (IPR2015-01284), 8,633,162 (IPR2015-01278), 8,642,556 (IPR2015-01286), and 8,685,930 (IPR2015-01283), but all were terminated before institution decisions. U.S. Application No. 15/011,159, filed January 29, 2016, claims the benefit of U.S. Application No. 14/222,478 (the '191 patent), which is a continuation, via U.S. Application Nos. 13/961,828 and 11/897,177, of the '857 application.

Petitioner also identifies the following pending, consolidated actions involving the '111 patent: (i) *Allergan, Inc. v. Innopharma, Inc.*, No. 2:15cv1504



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(E.D. Tex. filed Sept. 8, 2015) (EX 1025); (ii) *Allergan, Inc. v. Teva*

*Pharmaceuticals USA, Inc.*, No. 2:15-cv-01455 (E.D. Tex. filed Aug. 24, 2015)

(EX 1023); and (iii) *Allergan, Inc. v. Famy Care Ltd.*, No. 16-00401 (E.D. Tex.

filed Apr. 12, 2016) (EX 1026).

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

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#### **IV. STATEMENT OF PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED**

Petitioner requests review of claims 1-27 of the '111 patent under 35 U.S.C.

§ 311 and AIA § 6 and that each claim be canceled as unpatentable:

Ground	Claims	Description
1	1-27	Anticipated under §102 by Ding '979
2	1-27	Obvious under §103 over Ding '979 and Sall
3	11 and 16	Obvious under §103 over Ding '979, Sall, and Acheampong

## V. STATEMENT OF NON-REDUNDANCY

Each Ground raised in this Petition is meaningfully distinct. Ground 1 asserts anticipation of claims 1-27 based on Ding '979. Ground 2 asserts obviousness of claims 1-27 based on Ding '979 and Sall. Sall expressly teaches certain intrinsic properties of the claimed emulsion, including efficacy, relative efficacy, and substantially no detectable blood concentration at trough levels, and provides additional reasons to make and use the claimed emulsion to treat dry eye disease. Ground 3 asserts obviousness of dependent claims 11 and 16 based on Ding '979, Sall, and Acheampong. Acheampong expressly teaches the claimed emulsion results in substantially no detectable blood concentration at trough and peak levels.

## VI. CLAIM CONSTRUCTION

In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, No. 15-446, 2016 WL 1626647 (U.S. June 20, 2016). Claim terms are also “generally given their ordinary and customary meaning,” which is the meaning that the term would have to a person of ordinary

skill in the art at the time of the invention in view of the specification. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Under either standard, there is a reasonable likelihood that Petitioner will prevail with respect to the challenged claims. A few terms are discussed below.

**A. “Buffer”**

The term “buffer” appears in claims 4-6, 9-10, and 13-14 of the ’111 patent. Claims 5, 10, and 14 recite “the buffer is sodium hydroxide.” The patent states that “[t]he pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide ... to a physiological pH level.” EX1001, 12:17-18. In light of the specification, the broadest reasonable interpretation of the term “buffer” includes sodium hydroxide. EX1002, ¶38.

**B. “Substantially No Detectable Concentration”**

The term “substantially no detectable concentration” appears in claims 11 and 16 of the ’111 patent with regard to measuring CsA in human blood. According to the specification, cyclosporin concentration is preferably determined “using a liquid chromatography-mass spectroscopy-mass spectroscopy,” which has a cyclosporin component detection limit of 0.1 ng/mL.” EX1001, 5:65–6:4. Concentrations lower than “0.1 ng/ml are therefore considered substantially undetectable.” *Id.* A skilled artisan could measure blood concentration at either peak or trough levels. EX1002, ¶39. Accordingly, the broadest reasonable

interpretation of the phrase “substantially no detectable concentration” includes a blood concentration below 0.1 ng/mL measured at either peak or trough levels.

**C. “Effective” and “Therapeutically Effective”**

Dependent claims 17 and 20-27 state the emulsion is “effective” or “therapeutically effective” in increasing tear production, treating dry eye disease, or treating KCS. The ’111 patent characterizes KCS as “an absolute or partial deficiency in aqueous tear production.” EX1001, 3:3-6. This is consistent with its plain meaning. EX1022 at 0003 (KCS is an “inflammation of the conjunctiva and of the cornea” that is “associated with decreased tears” and is a species of, and is often used interchangeably with, or as a partial synonym of, dry eye disease); EX1002, ¶¶40-41. During prosecution, Patent Owner relied on an increase in tearing to assert unexpected therapeutic efficacy of the claimed emulsion for treating dry eye disease/KCS. EX1004, 0253; EX1002, ¶42. The plain meaning of the word “therapeutic” includes palliative (remediating) treatments as well as curative treatments. EX1002, ¶¶43-44; EX1022 at 0007 (therapeutic), 0004 (palliative), 0005 (remedy). Thus, in the context of the ’111 patent, an emulsion that is effective in increasing tear production is an example of an emulsion therapeutically effective in treating dry eye disease/KCS.

## **VII. BACKGROUND KNOWLEDGE IN THE ART PRIOR TO SEPTEMBER 15, 2003**

The background publications below reflect knowledge skilled artisans would bring to bear in reading the prior art at the time of the invention, *i.e.*, September 15, 2003, and thereby assist in understanding why one would have been motivated to combine or modify the references as asserted in this Petition. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1364 (Fed. Cir. 2015). The knowledge of a skilled artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious. *KSR*, 550 U.S. at 406; *Genzyme Therapeutic Prods. Ltd. P'ship v. Biomarin Pharm. Inc.*, Nos. 2015-1720, -1721, slip op. at 9-14 (Fed. Cir. June 14, 2016); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

Prior to September 15, 2003, it was known that inflammation contributed to dry eye diseases such as KCS. *E.g.*, K. Kunert *et al.*, *Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome* 118 Archives of Ophthalmology 1489 (2000) (“Kunert,” EX1012); EX1002, ¶47. CsA, a known anti-inflammatory agent, had been shown to significantly reduce inflammation markers associated with dry eye upon topical ophthalmic administration. EX1012, 1489; EX1002, ¶48. Dry eye disease was defined in the art as, “a deficiency in either the aqueous or mucin components of the precorneal tear film. The most

commonly encountered aqueous-deficient dry eye in the United States is [KCS].”

*Medications for Dry Eye* (1999) in Physicians’ Desk Reference for Ophthalmology (27th ed.) Montvale, NJ: PDR Network (“Ophthalmic PDR,” EX1013) at 13. The Ophthalmic PDR also notes that a topical CsA therapy, Sandimmune<sup>®</sup>, was readily available and was prescribed for ocular disorders including conjunctivitis and keratitis. *Id.* at 18; EX1002, ¶49.

Clinical trials establishing the efficacy and safety of CsA-in-castor oil emulsions for treatment of dry eye disease/KCS were known prior to September 2003. EX1002, ¶48. Several clinical studies were performed in the late 1990’s and early 2000’s. For example, Kunert established a decrease in lymphocyte activation markers after topical ophthalmic administration of a 0.05% CsA in a castor oil emulsion, teaching that treatment with 0.05% CsA in castor oil “may help to reduce the pathophysiological factors contributing to the development of KCS.” EX1012, 1495. Turner established that the 0.05% CsA-in-castor oil emulsion was at least as effective in decreasing inflammation markers as the 0.10% CsA-in-castor oil emulsion. K. Turner *et al.*, *Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion* 19 *Cornea* 492, 492 (2000) (EX1014); EX1002, ¶¶48, 51. Stevenson conducted a Phase 2 clinical trial, and states that 0.05% and 0.10% CsA-in-castor oil emulsions were “the most appropriate

formulations . . . because no additional benefits were observed with the higher concentrations.” D. Stevenson *et al.*, *Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease* 107 Ophthalmology 967, 967 (2000) (“Stevenson,” EX1015).

It was further known that, for effective topical ophthalmic treatment, “[t]issue concentrations [of CsA] in excess of minimal therapeutic levels (50 to 300 ng CsA/g tissue)” must be achieved. R. Kaswan, *Intraocular Penetration of Topically Applied Cyclosporine*, 20 Transplantation Proceedings 650, 652 (1988) (“Kaswan,” EX1011). Tissue concentrations well in excess of this therapeutic range were achieved by Kaswan following topical ophthalmic administration of CsA in an olive oil emulsion. It was known in the art, however, that “CsA [in] castor oil drops resulted in higher concentrations of the drug in the aqueous humor and cornea than when CsA [in] olive oil drops were used.” A. Kanpolat *et al.*, *Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration* 20 CLAO J. 119, 121 (1994) (“Kanpolat,” EX1018); EX1002, ¶51. As Allergan’s experts conceded during prosecution, “[i]t was known in the art at the time this application was filed that cyclosporin could be administered topically locally to the eye to target and treat dry eye by using cyclosporin A’s immunomodulatory properties[.]” EX1004, 0248, 0272-73; EX1002, ¶¶123-24.

Castor oil vehicles were used for topical ophthalmic administration of highly lipophilic compositions, like CsA, that must be formulated in a water-solubilized form. U.S. Patent No. 5,981,607 to Ding *et al.*, filed January 20, 1998 (“Ding ’607,” EX1010); EX1002, ¶50 (discussing Gerald Hecht, *Ophthalmic Preparations*, in *Remington: The Science And Practice Of Pharmacy* 821 (A. Gennaro ed. 2003) (“Remington,” EX1016)); E. Goto *et al.*, *Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction* 109 *Ophthalmology* 2030 (2002) (“Goto,” EX1017). Methods for determining the optimal ratio of oil-to-drug were well established in the art prior to September 2003. U.S. Patent No. 5,578,586 to Glonek *et al.* (“Glonek,” EX1009).

Ding ’607 (EX1010) discloses topical ophthalmic emulsions containing castor oil for the “treatment of keratoconjunctivitis sicca (dry eye) syndrome.” EX1010, 6:25-26. Ding ’607 teaches that these emulsions possess “a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues,” *id.* at 3:32-36, and that additional active agents can be added to increase the therapeutic efficacy of the emulsion. *Id.* at 3:48-52; EX1002, ¶¶53-54. Ding ’607 reports significant improvement in KCS severity as measured by various tests such as the Schirmer Tear Test, as well as corneal and conjunctival staining. Ding ’607 further establishes a correlation between the amount of castor



oil in the emulsion and the mean ocular residence time of the emulsion, teaching, “long retention of the higher fatty acid glyceride [castor oil] when the emulsion is instilled into an eye. This in turn can retard water evaporation from the eye which alleviates dry eye symptoms.” EX1010, 3:66–4:3; EX1002, ¶54.

Clinical trials conducted before September 2003 also established that castor oil provided a “large therapeutic effect” to patients suffering from KCS. *E.g.*, EX1014, 492; EX1015, 973; EX1002, ¶55. This “therapeutic effect of the [castor] oil-in-water vehicle” was “expected, as topical application of certain lipid mixtures can accelerate epidermal barrier recovery after defined barrier insults in mice.” EX1014, at 496. Further, the art also identified the anti-inflammatory properties of ricinoleic acid, the main component of castor oil, accounting for about 90% of castor oil, in providing direct relief of chronic dry eye syndromes. *E.g.*, A. Vieira *et al.*, *Effect of Ricinoleic Acid in Acute and Subchronic Experimental Models of Inflammation*, 9 *Mediators of Inflammation* 223 (2000) (“Vieira,” EX1019); EX1002, ¶55. Vieira states, “topical application of ricinoleic acid (RA), the main component of castor oil, exerts remarkable analgesic and anti-inflammatory effects.” EX1019, 223; EX1002, ¶55.

The efficacy of the castor oil vehicle described in Turner (EX1014) was said to have led to denial of regulatory approval for Allergan’s dry eye treatment Restasis® in the late 1990’s. EX1002, ¶56; R. Murphy, *The Once and Future*

*Treatment of Dry Eye*, Review of Optometry 1, 5 (2000) (“Murphy,” EX1020). As Allergan was unable to demonstrate a statistically significant improvement using Restasis<sup>®</sup> compared to the vehicle, the committee recommended against FDA-approval. Murphy concluded: “In the meantime, someone should consider packaging castor oil as a treatment for dry eye. Apparently it’s the next best thing to cyclosporin.” EX1020, at 5.

Thus, drug emulsions comprising CsA and castor oil were well known in the art to provide effective therapeutic relief of dry eye disease/KCS by significantly reducing inflammation and increasing tear production. EX1002, ¶57, discussing Kunert, EX1012; Turner, EX1014; Stevenson, EX1015; Ding ’607, EX1010.

It was also well known in the art by September 15, 2003, that elevated concentrations of CsA in the bloodstream correlated with, and could result in, serious adverse effects in a patient. EX1002, ¶¶52, 58 (discussing Small *et al.*, *Blood Concentrations of Cyclosporin A During Long-Term Treatment with Cyclosporin A Ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease* 18 J. Ocular Pharmacology & Therapeutics 411 (2002) (“Small,” EX1021)). Thus, blood concentrations of CsA were routinely measured, using liquid chromatography-tandem mass spectrometry, to determine if blood levels of CsA were elevated. *Id.* Small states that treatment of KCS with topical ophthalmic emulsions of CsA requires 2600-fold lower dosage than systemic

treatment, and that the lower required dosages, such as 0.05% CsA in a castor oil emulsion, produces “practically undetectable” levels of CsA in the blood, based on a quantification limit of 0.1 ng/mL. *Id.* at 411-12.

## **VIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY**

### **A. [Ground 1] Claims 1-27 are Anticipated under 35 U.S.C. § 102(b) by Ding ’979**

Ground 1 establishes by a preponderance of the evidence that Ding ’979 (EX1006) anticipates the emulsion recited in claims 1-27 of the ’111 patent under 35 U.S.C. § 102(b).

#### **1. Claims 1-10, 12-15, and 18-19**

Independent claims 1, 13, and 18 each recite a topical ophthalmic emulsion comprising 0.05% CsA, 1.25% castor oil, and other excipients. The discussion that follows uses the elements and organization recited in claims 18 and 19 because they are narrower than claims 1-10 and 12-15. The teachings rendering claims 18 and 19 unpatentable also render claims 1-10 and 12-15 unpatentable. *In re Muchmore*, 433 F.2d 824, 824-25 (C.C.P.A. 1970) (“Since we agree with the board’s conclusion of obviousness as to these narrow claims, the broader claims must likewise be obvious.”); *accord Soverain Software LLC v. Victoria’s Secret Direct Brand Mgmt., LLC*, 778 F.3d 1311, 1315 (Fed. Cir. 2015).

The elements of claims 1-10 and 12-15 comparable to the elements of claims 18 and 19 are shown in the comparative table below, EX1002, ¶90, where particular clauses and elements have been given item numbers for convenient reference:

<b>Item</b>	<b>Claim 18</b>	<b>Claim 13</b>	<b>Claim 1</b>
<b>I</b>	A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic emulsion comprising:	A topical ophthalmic emulsion for treating an eye of a human, wherein the topical ophthalmic emulsion comprises:	A topical ophthalmic emulsion for treating an eye of a human comprising
<b>II</b>	cyclosporin A in an amount of about 0.05% by weight;	cyclosporin A in an amount of about 0.05% by weight;	cyclosporin A in an amount of about 0.05% by weight,
<b>III</b>	castor oil in an amount of about 1.25% by weight;	castor oil in an amount of about 1.25% by weight;	<b>Item IX</b> below
<b>IV</b>	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80, <b>Claim 7</b> (about 1.0% by weight)
<b>V</b>	acrylate/C10-30 alkyl acrylate cross-polymer in an amount of 0.05% by weight;	acrylate/C10-30 alkyl acrylate cross-polymer in an amount 25 of about 0.05% by weight;	acrylate/C10-30 alkyl acrylate cross-polymer, <b>Claim 8</b> (0.05%)
<b>VI</b>	glycerine in an amount of about 2.2% by weight;	a tonicity component or a demulcent component in an amount of about 2.2% by weight; <b>Claim 15</b> (glycerine)	<b>Claims 2</b> (tonicity/demulcent agent); <b>3, 6</b> (glycerine); and <b>9-10</b> (about 2.2% by weight)
<b>VII</b>	sodium hydroxide;	a buffer; and	<b>Claims 4, 6, 9</b> (buffer)

	and	<b>Claim 14</b> (sodium hydroxide)	and <b>5, 10</b> (sodium hydroxide)
<b>VIII</b>	water;	water;	water,
<b>IX</b>	<b>Item III</b> above	<b>Item III</b> above	and castor oil in an amount of about 1.25% by weight; and
<b>X</b>	wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.	wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.	wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.
<b>XI</b>	<b>Claim 19</b> (pH in the range of about 7.2 to about 7.6)	wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6 and	<b>Claim 12</b> (pH in the range of about 7.2 to about 7.6)

The following explanation identifies where each element of each Item of the above table is found in Ding '979 for independent claims 1, 13, and 18. The same analysis addresses the corresponding dependent claims in the above table.

Regarding **Item I** from the table above, Ding '979 discloses non-irritating CsA-in-castor oil emulsions for treatment of [KCS] “(dry eye) syndrome” that are “suitable for topical application to ocular tissue.” EX1006, 5:9-11; *id.* at 6:3-7; EX1002, ¶¶61, 91. Moreover, Ding '979 teaches that CsA increases tear production in the eye and has been found effective in treating dry eye disease/KCS. EX1006, 1:10-16, 37-39. By teaching the topical administration of the CsA-containing emulsions of Ding '979 to a human eye to increase tear production and to treat dry eye

disease/KCS, Ding '979 satisfies “topical ophthalmic emulsion for treating an eye of a human” (**Item I**) of claims 1-10, 12–15, 18, and 19. EX1002, ¶¶61, 68, 91.

The emulsions disclosed in Ding '979 contain every ingredient of the emulsion recited in claims 1-27 as shown in Items II-XI in the table above. The emulsion ingredients in Example 1 of Ding '979 are shown below:

	<u>Example 1</u>				
	A	B	C	D	E
Cyclosporin A	0.40%	0.20%	0.20%	0.10%	0.05%
Castor oil	5.00%	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%	2.20%
NaOH	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

EX1006, 4:32-43. Examples 1A-E of Ding '979 illustrate the castor oil and CsA percentage ranges recited in claims 7 and 8 of Ding '979. As Dr. Bhagwat explains, Examples 1A-E would be effective in treating dry eye disease and indeed at least examples 1A-D are said in Ding '979 to be effective. EX1006, 5:18-28; EX1002, ¶71; EX1005, 0435-37 (applicants conceding “error” in its argument that Example 1E would not be effective at treating dry eye).

Ding '979 discloses each ingredient and also the percentage of each ingredient in the emulsion of claims 1-27 of the '111 patent. The 1.0% polysorbate

80 ingredient in Ding '979 (*e.g.*, Example 1) meets the polysorbate 80 limitation of claims 1-27, and is the precise percentage recited in claims 7, 13-19, and 23-27

**(Item IV).** EX1002, ¶¶92-93. Pemulen<sup>®</sup> is an “acrylate[ ]/C10-30 alkyl acrylate cross-polymer” (EX1006, 4:4-5), and thus Ding '979 (Example 1, at 0.05%)

teaches the acrylate/C-10-30 alkyl acrylate cross-polymer as recited in claims 1-27 and the 0.05% weight percentage limitation in claims 8, 13-19, and 23-27

**(Item V).** EX1002, ¶¶92-93. Glycerine satisfies the tonicity/demulcent agent/component or glycerine elements as recited in claim 2-3, 6, 9, 13, 15, 18 and dependent claims of the '111 patent (EX1001, 12:45 - 47), and the 2.2%

percentage of claims 9-10, and 13-27 **(Item VI)** is shown in each emulsion of

Example 1. *Id.* Sodium hydroxide of *e.g.*, the Ding '979 Example 1 emulsions, satisfies the buffer and sodium hydroxide elements recited in claims 4-6 and 9-10, 13-19, and 23-27 **(Item VII)**. *Id.* The water ingredient in Ding '979 Example 1 emulsions satisfies the water element of claims 1-27 **(Item VIII)**. *Id.*

Example 1 of Ding '979 discloses the emulsions have a pH of 7.2-7.6, thereby satisfying the pH range element of claims 12, 13, and 19 **(Item XI)**.

EX1002, ¶¶93, 97. Additionally, each of the emulsions taught by Ding '979 contain CsA as the only peptide present **(Item X)**. EX1006, 4:32-43. Indeed, claim 8 of Ding '979 provides for an emulsion “consisting of” CsA and other, non-peptide, ingredients. EX1006, 6:35-41; EX1002, ¶98. Accordingly, Ding '979

teaches topical ophthalmic emulsions wherein CsA is the only peptide present in the emulsion.

Ding '979 also satisfies the weight percentages of CsA and castor oil claimed in claims 1-27 of the '111 patent. Example 1 specifies that the percentage of CsA may be 0.05% (**Item II**) and the percentage of castor oil may be 1.25% (**Items III and IX**). EX1006, 4:32-43; EX1002, ¶¶91, 94. A skilled artisan would have at once envisaged the CsA/castor oil amounts in the claimed combination, *i.e.*, 0.05% CsA and 1.25% castor oil. EX1002, ¶94. Ding '979 provides four castor oil emulsion vehicles, Examples 2A-D. Example 2C discloses each ingredient of the claimed emulsion, with the sole exception of the CsA concentration.

Example 2

	A	B	C	D
Castor oil	5.00%	2.50%	1.25%	0.625%
Polysorbate 80	1.00%	1.00%	1.00%	1.00%
Pemulen®	0.05%	0.05%	0.05%	0.05%
Glycerine	2.20%	2.20%	2.20%	2.20%
NaOH	Qs	qs	qs	qs
Purified water	Qs	qs	qs	qs
pH	7.2-7.6	7.2-7.6	7.2-7.6	7.2-7.6

EX1006, 4:44-53.

Ding '979 also teaches preferred CsA concentrations for particular castor oil emulsions. Ding '979 teaches that the preferred ratio of CsA to castor oil is below



0.16, and more preferably between 0.02 and 0.12. EX1006, 3:16-20. Example 1 presents five example emulsions (A-E) that include CsA in the four castor oil vehicles disclosed in Example 2. The emulsions each have a CsA-castor oil ratio within the more preferred range as taught at 3:16-20 of EX1006. EX1002, ¶64. Based on the four castor oil vehicles of Example 2, only two additional emulsions with the CsA percentages of Example 1 are possible within the “more preferred” range: an emulsion having 0.05% CsA/1.25% castor oil, and an emulsion having 0.1% CsA/2.5% castor oil. *Id.* As explained by Dr. Bhagwat, the skilled artisan would at once envisage these two emulsions as being taught by Ding ’979, and would reasonably expect them to be therapeutically effective for treating dry eye disease as discussed below. EX1002, ¶71.

Example 1 further defines an even narrower range of ratios of CsA to castor oil, as Examples 1A-E have ratios of either 0.08 or 0.04. EX1002, ¶94. As discussed by Dr. Bhagwat, a person of ordinary skill in the art would have expected that any of the CsA amounts disclosed in Example 1, in combination with any of the vehicles disclosed in Example 2, would be effective in the treatment of dry eye disease if the ratio of CsA to castor oil falls within the preferred range taught by Ding ’979. EX1002, ¶¶71, 94. For Ding ’979 Example 2C, only two CsA percentages from Example 1 fall within both the preferred and Example 1 ratio range: 0.05% CsA and 0.10% CsA. The 0.10% CsA was combined with the

1.25% castor oil vehicle in Example 1 (emulsion D), and the other, 0.05% CsA, the Patent Owner previously conceded, “is *squarely within the teaching of the Ding reference*, and the Office should disregard any statements by the applicants suggesting otherwise[.]” EX1005, 0435 (emphasis added); EX1002, ¶¶18, 95.

Thus, Ding ’979 anticipates claims 1-10, 12-15, and 18-19. A claim chart which identifies the relevant teachings of Ding ’979 to each element of these claims is provided below.

## 2. Claims 17 and 20-27

Claims 17 and 20-27 depend from claims 1, 13, and 18. The discussion above with respect to the emulsion of claims 1, 13, and 18 applies equally to claims 17 and 20-27 because these claims merely further recite treatment of a related dry-eye condition, each of which is fully disclosed in Ding ’979. For example, claim 17 depends from claim 13, and further recites “the topical ophthalmic emulsion is effective in treating keratoconjunctivitis sicca.” Claims 23 and 24 similarly depend from claim 13 and recite that the emulsion is “therapeutically effective at treating dry eye” and “therapeutically effective in increasing tear production.” Claims 20-22 and 25-27 similarly recite that the emulsion of claims 1 and 18 are therapeutically effective for the treatment of dry eye disease or KCS, or for increasing tear production.

Ding '979 teaches the therapeutic efficacy of its CsA-in-castor oil emulsions for treating dry eye disease/KCS and for increasing tear production. For example, Ding '979 discloses non-irritating CsA-in-castor oil emulsions “for treatment of keratoconjunctivitis sicca (dry eye) syndrome” that are “suitable for topical application to ocular tissue.” EX1006, 5:9-11; *id.* at 6:3-7; EX1002, ¶¶61, 69, 91, 99. Ding '979 teaches that cyclosporins have “known immunosuppressant activity . . . effective in treating immune mediated [*sic*, mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.” EX1006, 1:10-16; EX1002, ¶99. Additionally, Ding '979 teaches that the cyclosporins’ activity “is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.” EX1006, 1:37-39; EX1002, ¶99. Thus, Ding '979 discloses that the CsA/castor oil emulsions of Ding '979 are effective in treating dry eye disease and KCS and at increasing tear production in the eye, thereby satisfying the elements recited in claims 17 and 20-27. EX1002, ¶99.

### 3. Claims 11 and 16

Claims 11 and 16 depend from claims 1 and 13, and each recite “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”

As explained by Dr. Bhagwat, the fact that when the emulsion is administered to the eye there is “substantially no detectable concentrations of

cyclosporin A” in the blood is simply a known property of the emulsion when given at its recommended dose. EX1002, ¶100. Prior art publications confirm Dr. Bhagwat’s explanation. EX1021, 411 (“No patient receiving 0.05% CsA [in-castor oil emulsion] had any quantifiable CsA in the blood.”); EX1007, 637 (same); EX1008 at 1004 (same). Thus, reciting the concentration of CsA in blood following topical administration fails to further limit the emulsion of claims 1 and 13, and claims 11 and 16 are anticipated by Ding ’979 for the same reasons.

As discussed above, all ingredients of the claimed emulsion are identified in Ding ’979 for use together in the same emulsion for the same therapeutic indication, with percentages for each ingredient taught expressly by Ding ’979. The claim chart below shows how Ding ’979 discloses each element of claims 1-27, and includes reference to the supporting explanation by Dr. Bhagwat (EX1002). “Item” numbers are those from the table above, comparing independent claims 1, 13, and 18.

<b>Challenged Claims</b>	<b>Anticipated by Ding ’979</b>
1. A topical ophthalmic emulsion for treating an eye of a human comprising <b>[Item I]</b>	“[A] non-irritating emulsion ... suitable for topical application to ocular tissue.” EX1006, 6:3-7; EX1002, ¶¶61-63, 68, 91.
cyclosporin A in an amount of about 0.05% by weight, <b>[Item II]</b>	EX1006, 4:33-43, Example 1E and claims 7-8; EX1002, ¶¶64-66, 91-92.

<p>polysorbate 80</p> <p><b>[Item IV]</b></p>	<p>Examples 1A-E, comprising 1.00% polysorbate 80. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>
<p>acrylate/C10-30-alkyl acrylate cross-polymer,</p> <p><b>[Item V]</b></p>	<p>Examples 1A-E, comprising 0.05% Pemulen<sup>®</sup>. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p> <p>“Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers.” EX1006, 4 :4-5; EX1002, ¶¶64, 93.</p>
<p>water,</p> <p><b>[Item VIII]</b></p>	<p>Examples 1A-E, comprising water. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>
<p>and castor oil in an amount of about 1.25% by weight;</p> <p><b>[Items III and IX]</b></p>	<p>“More preferably ... the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.” EX1006, 3:17-20.</p> <p>Examples 1D and 2C, comprising 1.25% castor oil. EX1006, 4:33-54; EX1002, ¶¶64-66, 91-94.</p> <p>Example 1B, comprising a 0.04 ratio of CsA-to-castor oil. EX1006, 4:33-43; EX1002, ¶¶67, 94-95.</p>
<p>wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.</p> <p><b>[Item X]</b></p>	<p>Examples 1A-E, which comprise CsA as the only peptide present in the ophthalmic emulsions. EX1006, 4:33-43; EX1002, ¶98.</p>
<p>2. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises a tonicity agent or demulcent component.</p> <p>3. The topical ophthalmic emulsion of claim 2, wherein the tonicity agent or the demulcent component is glycerine.</p>	<p>Claim 1 in the claim chart above.</p> <p>Examples 1A-E, comprising 2.20% glycerine. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>

<b>[Item VI]</b>	
<p>4. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises a buffer.</p> <p>5. The topical ophthalmic emulsion of claim 4, wherein the buffer is sodium hydroxide.</p> <p>6. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises glycerine and a buffer.</p>	<p>Claim 1 in the claim chart above.</p> <p>Examples 1A-E, comprising sodium hydroxide. EX1006, 4 :33-43; EX1002, ¶¶64-66, 92-93.</p> <p>Examples 1A-E, comprising 2.20% glycerine. EX1006, 4 :33-43; EX1002, ¶¶64-66, 92-93.</p>
<b>[Item VII]</b>	
<p>7. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion comprises polysorbate 80 in an amount of about 1.0% by weight.</p> <p><b>[Item IV]</b></p>	<p>Claim 1 in the claim chart above.</p> <p>Examples 1A-E, comprising 1.00% polysorbate 80. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>
<p>8. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion comprises acrylate.C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight.</p> <p><b>[Item V]</b></p>	<p>Claim 1 in the claim chart above.</p> <p>Examples 1A-E, comprising 0.05% Pemulen<sup>®</sup>. EX1006, 4 :33-43; EX1002, ¶¶64-66, 92-93.</p> <p>“Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers.” EX1006, 4 :4-5; EX1002, ¶¶64, 93.</p>
<p>9. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion further comprises glycerine in an amount of about 2.2% by weight, water, and a buffer.</p> <p>10. The topical ophthalmic emulsion of claim 9, wherein the buffer is sodium hydroxide.</p>	<p>Claim 1 in the claim chart above.</p> <p>Examples 1A-E, comprising 2.20% glycerine, water, and sodium hydroxide. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>

<b>[Item VII]</b>	
11. The topical ophthalmic emulsion of claim 1, wherein, when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.	<p>Claim chart for claim 1, above.</p> <p>Inherent intrinsic property of the formulation, <i>supra</i>.</p>
12. The topical ophthalmic emulsion of claim 6, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.  <b>[Item XI]</b>	<p>Examples 1A-E, comprising pH values of 7.2 – 7.6. EX1006, 4:33-43; EX1002, ¶¶64, 95.</p>
13. A topical ophthalmic emulsion for treating an eye of a human, wherein the topical ophthalmic emulsion comprises <b>[Item I]</b> : cyclosporin A in an amount of about 0.05% by weight <b>[Item II]</b> ; castor oil in an amount of about 1.25% by weight <b>[Items III and IX]</b> ; polysorbate 80 in an amount of about 1.0% by weight <b>[Item IV]</b> ; acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight <b>[Item V]</b> ; a tonicity component or a demulcent component in an amount of about 2.2% by weight <b>[Item VI]</b> , a buffer <b>[Item VII]</b> ; and water <b>[Item VIII]</b> ; wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6 <b>[Item XI]</b> and wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion <b>[Item X]</b> .  14. The topical ophthalmic emulsion of claim 13, wherein the buffer is sodium hydroxide <b>[Item VII]</b> .	<p>Claim chart for claims 1-10, and 12, above.</p>

15. The topical ophthalmic emulsion of claim 13, wherein the tonicity component or the demulcent component is glycerine [ <b>Item VI</b> ].	
16. The topical ophthalmic emulsion of claim 13, wherein. When the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.	Claim 11 in the claim chart above.
17. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion is effective in treating keratoconjunctivitis sicca.	<p>“The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome.” EX1006, 5:9-11; EX1002, ¶¶61, 69, 91, 99.</p> <p>“Cyclosporins [have] ... known immunosuppressant activity ... effective in treating immune mediated [sic: mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.” EX1006, 1:10-16; EX1002, ¶¶61, 69, 91, 99.</p>
18. A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic emulsion comprising [ <b>Item I</b> ]: cyclosporin A in an amount of about 0.05% by weight [ <b>Item II</b> ]; castor oil in an amount of about 1.25% by weight [ <b>Items III and IX</b> ]; polysorbate 80 in an amount of about 1.0% by weight [ <b>Item IV</b> ]; acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight [ <b>Item V</b> ]; glycerine in an amount of about 2.2% by weight [ <b>Item VI</b> ]; sodium hydroxide [ <b>Item VII</b> ]; and water [ <b>Item VIII</b> ]; wherein cyclosporin A is the only	Claim chart for claims 1-10, and 12, above.



<p>peptide present in the topical ophthalmic emulsion [<b>Item X</b>].</p> <p>19. The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.</p> <p style="text-align: center;"><b>[Item XI]</b></p>	
<p>20 The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.</p> <p>21. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.</p> <p>22. The topical ophthalmic emulsion of claim 1, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.</p>	<p>Claim chart for claims 1 and 17, above.</p> <p>“The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.” EX1006, 1:37-39; EX1002, ¶¶61, 69, 91, 99.</p>
<p>23. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye.</p> <p>24. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.</p>	<p>Claim chart for claims 13, 17, and 20-22, above.</p>
<p>25. The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion is therapeutically effective in treating dry eye disease.</p> <p>26. The topical ophthalmic emulsion of</p>	<p>Claim chart for claims 17, 18, and 20-22, above.</p>

claim 18, wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.	
27. The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.	

**B. [Ground 2] Claims 1-27 are Obvious under 35 U.S.C. § 103 over Ding '979 and Sall**

Claims 1-27 would have been obvious to a person of ordinary skill in the art based on Ding '979 further in view of Sall (EX1007). An artisan would look to Ding '979 together with Sall because both describe non-irritating, therapeutically effective, topical, ophthalmic, castor oil emulsions suitable for delivery of 0.05% and 0.10% CsA for increasing tear production and treating dry eye disease/KCS. EX1002, ¶106.

1. Claims 1-16, and 18-19

The teachings of Ding '979 are discussed above. EX1002, ¶¶103-05. Sall provides further motivation to make the 0.05% CsA/1.25% castor oil topical ophthalmic emulsion of Ding '979, and expressly describes the “substantially no detectable [blood] concentration” of CsA found in claims 11 and 16.

Sall describes a “multicenter, randomized, double-masked” Phase 3 clinical trial. EX1007, 632; EX1002, ¶¶73, 106. The trial involved the parallel assessment

of the efficacy and safety of 0.05% and 0.10% CsA-in-castor oil emulsions as compared to a control vehicle (the same castor oil emulsion that did not contain CsA). EX1007, 632. One of the CsA/castor oil emulsions, or the control vehicle, was administered twice daily to patients. *Id.* Sall concluded that both the 0.05% and the 0.10% CsA emulsions “were safe and effective in the treatment of moderate to severe dry eye disease yielding improvements in both objective and subjective measures.” *Id.* at 631; EX1002, ¶¶74, 81, 107-08. Sall reported that treatment with either percentage of CsA provided “significantly ( $p \leq 0.05$ ) greater improvements than vehicle” for treating dry eye disease, when measured by corneal staining and Schirmer values, and further noted that there was “no dose-response effect” between the two percentages of CsA. EX1007, 637. Thus, Sall teaches either concentration of CsA is “effective” or “therapeutically effective” in increasing tear production and treating dry eye disease/KCS (claims 17, 20-27). In addition to teaching that the 0.05% CsA emulsion is at least as effective as the 0.10% CsA emulsion, Sall also provides a strong rationale to deliver 0.05% CsA using the 1.25% castor oil vehicle taught by Ding ’979 (Example 2C). EX1007, 632; EX1002, ¶¶81-82, 111-13. Sall uses the same vehicle for delivering both 0.05% and 0.10% CsA. EX1007, Figs. 1-4 (showing a single vehicle control group for comparison to both the 0.05% and 0.10% CsA emulsion), 632 (“compare two concentrations of CsA ophthalmic emulsion to its vehicle”), 638 (stating that “the

vehicle, ... contributed to the overall improvements observed in all treatment groups in this study”); EX1002, ¶¶83, 112. Of the castor oil vehicles disclosed in Example 2 of Ding ’979, only vehicle C (1.25% castor oil) and vehicle D (0.625% castor oil) are used with emulsions in Example 1 having either 0.05% or 0.10% CsA. EX1006, 4:32-54.

The 1.25% castor oil vehicle is the only vehicle from Ding ’979 Example 2 for which both 0.05% and 0.10% CsA have a ratio of CsA-to-castor oil inside Ding ’979’s more preferred range of between 0.12 and 0.02 (*id.* at 3:17-20) and also within the ratio range found with each of the Example 1 emulsions (0.04-0.08). *Id.* Ding ’979 teaches that a 0.625% castor oil emulsion is not preferred for use with 0.10% CsA, because the ratio of CsA to castor oil would be 0.16, and Ding ’979 teaches that “[p]referably, the ... weight ratio of the cyclosporin to castor oil *is below 0.16.*” EX1006, 4:15-17 (emphasis added); EX1002, ¶113. In contrast, a 1.25% castor oil emulsion would have been suitable for use with both the 0.05% and 0.10% CsA emulsions, having CsA-to-castor-oil ratios of 0.04 and 0.08, respectively. *Id.* A skilled artisan would have formulated the 0.05% CsA/1.25% castor oil emulsion of Ding ’979 and administered it ophthalmically twice-daily, as Sall teaches. Selecting the 0.05% CsA percentage over the 0.10% CsA percentage would decrease the cost of production of the emulsion and reduce the potential for crystallization. EX1006, 3:58-63; EX1002, ¶110.

Given Ding '979 and Sall, a person of ordinary skill would have had a reasonable expectation that this emulsion would be effective in treating dry eye disease based on at least the success described by Sall: "Treatment with CsA, 0.05% or 0.1% gave significantly ( $P \leq 0.05$ ) greater improvements than vehicle in two objective signs of dry eye disease." *Id.* at 631; EX1002, ¶¶107-08. As Dr. Bhagwat explains, it would have been routine for a skilled artisan to make and confirm the efficacy of the emulsion comprising 0.05% CsA/1.25% castor oil. EX1002, ¶¶96, 116; EX1001, 14:14-16 ("These compositions are produced in accordance with well-known techniques[.]").

2. Claims 17, 20-27

Claims 17, 20-27 depend from claims 1, 13, and 18, and simply recite that the emulsion is "effective" or "therapeutically effective" in increasing tear production or in treating dry eye disease or KCS.

As discussed above, Sall teaches that the 0.05% CsA-in-castor oil emulsion is therapeutically effective in increasing tear production and in treating dry eye disease/KCS. EX1002, ¶107. Sall evaluated the therapeutic efficacy of twice-daily administration of topical, ophthalmic emulsions comprising CsA, at either 0.05% or 0.1%, with castor oil. EX1007, 632. In assessing the relative efficacies of the two CsA formulations, Sall measured corneal staining and the results of Schirmer Tear Tests, two objective clinical tests described in the prior art, EX1010,

6:34–7:23, and identified during prosecution of the '111 patent by Allergan expert Dr. Schiffman as, “key objective testing measures for dry eye or KCS,” EX1004, 0247. Sall reports, “[t]he novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease.” EX1007, 631; EX1002, ¶¶107-08. Sall also teaches that, after three months of treatment, the improvement in tear production as measured by the Schirmer Tear Test was “significantly greater” for the 0.05% CsA group as compared to the performance of the vehicle. EX1007, 635; EX1002, ¶77. Sall also noted that the 0.05% emulsion gave “significantly greater improvements” in three additional subjective measures of dry eye disease. EX1007, 635; EX1002, ¶¶78-79, 107-08. Thus, it would have been obvious in view of Ding '979 and Sall that the 0.05% CsA/1.25% castor oil emulsion would be therapeutically effective in treating both dry eye disease and keratoconjunctivitis and at increasing tear production in the eye, thereby satisfying the “emulsion is therapeutically effective in treating dry eye disease” as recited in claims 17 and 20-27. EX1002, ¶107.

### 3. Claims 11 and 16

Claims 11 and 16 depend from claims 1 and 13, and recite that “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”

Sall expressly teaches that when the 0.05% CsA-in-castor oil emulsion was administered to the human eye twice a day, it resulted in substantially no detectable concentration of CsA in the blood: “Trough blood concentrations of CsA ... below the limit of quantitation (of 0.1 ng/ml) in all samples.” EX1007, 637; EX1002, ¶¶114-15. Sall’s teachings are confirmed by numerous other background references. *E.g.*, EX1021, 411 (“No patient receiving 0.05% CsA [in castor oil emulsion] had any quantifiable CsA in the blood.”); EX1008, 1004 (same). Thus, based on Ding ’979 and Sall, it would have been obvious to a person of skill in the art that when the 0.05% CsA / 1.25% castor oil emulsion was administered to the eye the result would be substantially no detectable concentration of CsA in the blood.

Thus, Ding ’979 and Sall, along with the knowledge of the skilled artisan, render claims 1-27 obvious. EX1006, 4:32-43; EX1007, 631; EX1002, ¶116. The following claim chart shows in further detail how Ding ’979 and Sall render claims 1-27 obvious using exemplary claims 11, 17, 18 and 19, along with reference to supporting explanation in the declaration of Dr. Bhagwat (EX1002). Accordingly, claims 1-27 are unpatentable as obvious under 35 U.S.C. § 103.

<b>Exemplary Claims</b>	<b>Obvious over Ding ’979 and Sall</b>
11. The topical ophthalmic emulsion of claim 1, wherein, when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the	<i>See</i> claim chart for claim 1 in Ground 1. “Trough blood concentrations of CsA were below the limit of quantitation (of

<p>human has substantially no detectable concentration of cyclosporin A.</p>	<p>0.1 ng/ml) in all samples from the CsA 0.05% group.” EX1007, 637; EX1002, ¶¶80, 115.</p>
<p>17. The topical ophthalmic emulsion of claim 13, wherein the topical ophthalmic emulsion is effective in treating keratoconjunctivitis sicca.</p>	<p><i>See</i> claim chart for claim 13 in Ground 1.</p> <p>“The formulations set forth in Examples 1-4 were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome.” EX1006, 5:9-11; EX1002, ¶¶61, 69, 91, 99.</p> <p>“Cyclosporins [have] ... known immunosuppressant activity ... effective in treating immune mediated [<i>sic</i>: mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.” EX1006, 1:10-16; EX1002, ¶¶61, 69, 91, 99.</p> <p>“The novel ophthalmic formulations CsA 0.05% and 0.1% were safe and effective in the treatment of moderate to severe dry eye disease.” EX1007, 631 &amp; n.1; EX1002, ¶¶74, 107-08.</p> <p>“The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing.” EX1006, 1:37-39; EX1002, ¶¶61, 69, 91, 99.</p> <p>“Schirmer values ... with the CsA 0.05% group [were] significantly greater than the vehicle group.” EX1007, 635; EX1002, ¶¶76-77, 107.</p>
<p>18. A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic emulsion comprising:</p> <p style="text-align: center;"><b>[Item I]</b></p>	<p>“[A] non-irritating emulsion ... suitable for topical application to ocular tissue.” EX1006, 6:3-7; EX1002, ¶¶61-62, 68, 91.</p>



<p>cyclosporin A in an amount of about 0.05% by weight;</p> <p><b>[Item II]</b></p>	<p>EX1006, 4:33-43, Example 1E and claims 7-8; EX1002, ¶¶64-66, 91-92.</p> <p>“[P]atients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle.” EX1007, 631; EX1002, ¶¶73, 106.</p>
<p>castor oil in an amount of about 1.25% by weight;</p> <p><b>[Items III and IX]</b></p>	<p>“More preferably ... the weight ratio of cyclosporin to castor oil is between 0.12 and 0.02.” EX1006, 3:17-20.</p> <p>Examples 1D and 2C, comprising 1.25% castor oil. EX1006, 4:33-54; EX1002, ¶¶64-66, 91-94.</p> <p>Example 1B, comprising a 0.04 ratio of CsA-to-castor oil. EX1006, 4:33-43; EX1002, ¶¶67, 94-95.</p> <p>“Both the CsA emulsions and vehicle were sterile, nonpreserved castor oil in water emulsions.” EX1007, 632; EX1002, ¶¶73, 83.</p>
<p>polysorbate 80 in an amount of about 1.0% by weight;</p> <p><b>[Item IV]</b></p>	<p>Examples 1A-E, comprising 1.00% polysorbate 80. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>
<p>acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;</p> <p><b>[Item V]</b></p>	<p>Examples 1A-E, comprising 0.05% Pemulen<sup>®</sup>. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p> <p>“Pemulens are Acrylates/C10-30 Alkyl Acrylate Cross-Polymers.” EX1006, 4:4-5; EX1002, ¶¶64, 93.</p>
<p>glycerine in an amount of about 2.2% by weight;</p> <p><b>[Item VI]</b></p>	<p>Examples 1A-E, comprising 2.20% glycerine. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.</p>
<p>sodium hydroxide; and</p> <p><b>[Item VII]</b></p>	<p>Examples 1A-E, comprising sodium hydroxide. EX1006, 4:33-43; EX1002,</p>

	¶¶64-66, 92-93.
water;  <b>[Item VIII]</b>	Examples 1A-E, comprising water. EX1006, 4:33-43; EX1002, ¶¶64-66, 92-93.  “Both the CsA emulsions ... were sterile, nonpreserved castor oil in water emulsions.” EX1007, 632; EX1002, ¶¶73, 83.
wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.  <b>[Item X]</b>	Examples 1A-E, which comprise CsA as the only peptide present in the ophthalmic emulsions. EX1006, 4:33-43; EX1002, ¶98.
19. The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.  <b>[Item XI]</b>	Examples 1A-E, comprising pH values of 7.2 – 7.6. EX1006, 4:33-43; EX1002, ¶¶64, 95.

**C. [Ground 3] Claims 11 and 16 are Obvious under 35 U.S.C. § 103 over Ding ’979, Sall, and Acheampong**

Every element of claims 11 and 16 is taught through Ding ’979 (EX1006), Sall (EX1007), and Acheampong (EX1008). As discussed in Ground 2, claims 11 and 16 each recite “when the topical ophthalmic emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”

As explained in Ground 2, Sall teaches that humans receiving ophthalmic administrations of 0.05% CsA emulsions containing castor oil twice a day had, “[t]rough blood concentrations of CsA ... below the limit of quantitation (of 0.1

ng/ml) in all samples.” EX1007, 637; EX1002, ¶¶118-19. Acheampong adds to these teachings by describing a months-long study which evaluated both peak and trough CsA blood concentrations in humans receiving ophthalmic administrations of CsA/castor oil emulsions: “[S]ubjects with KCS received an eyedrop of vehicle or 0.05%, 0.1%, 0.2% or 0.4% cyclosporine emulsion twice daily. . . . Blood samples were collected . . . at morning troughs . . . [and] after the last dose.” EX1008, 1002. As presented in Table 1 of Acheampong, patients receiving ophthalmic emulsions of 0.05% CsA had no detectable concentration of CsA in the blood, at peak and trough levels. EX1008, 1002; EX1002, ¶¶120-21.

**Table 1.** Human blood trough and maximum cyclosporin A concentrations over 12 weeks

Cyclosporine emulsion	Range of blood cyclosporine A concentration (ng/ml)	
	Trough level	Maximum level
0.05%	<0.1	<0.1
0.1%	<0.1 to 0.102	<0.1
0.2%	<0.1 to 0.108	<0.1 to 0.144
0.4%	<0.1 to 0.157	<0.1 to 0.158

EX1008 at 1004. Acheampong and Sall together provide one of ordinary skill in the art with a reasonable expectation of success that, when the 0.05% CsA-in-castor oil emulsion is administered to the eye, there is “substantially no detectable concentration of cyclosporin A.” EX1002, ¶¶120-21.

Thus, dependent claims 11 and 16 of the '111 patent are obvious based on Ding '979, Sall, and Acheampong.

## **IX. NO OBJECTIVE INDICIA OF NON-OBVIOUSNESS**

During prosecution of the '111 patent, Allergan argued that objective indicia supported patentability. EX1004, 0235-44. To determine whether claims would have been obvious, one must consider “all evidence of obviousness and nonobviousness before reaching a determination.” *Wm. Wrigley Jr.*, 683 F.3d at 1365 n.5. A strong case of *prima facie* obviousness can outweigh any objective indicia of nonobviousness, however. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

During prosecution, Allergan submitted four declarations: two of which alleged “unexpected results,” EX1004, Schiffman Declaration, at 0246, Attar Declaration at 0272; one of which alleged commercial success of the FDA-approved drug Restasis<sup>®</sup>, EX1004, Mottiwala Declaration, at 0291; and one of which alleged a long-felt, unmet need existed prior to the alleged invention, EX1004, at 0301.

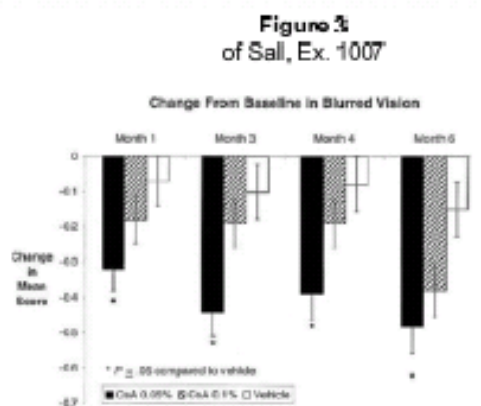
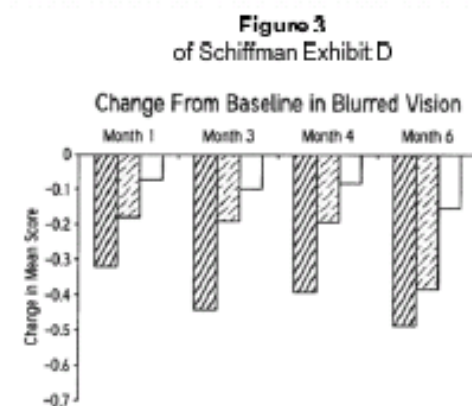
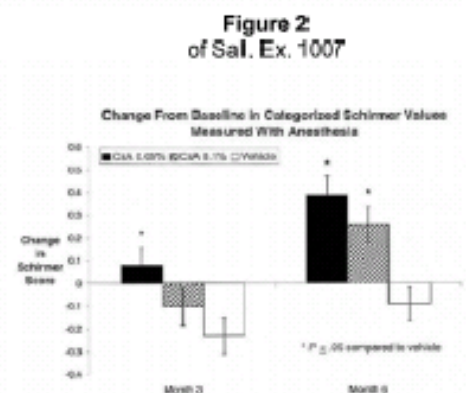
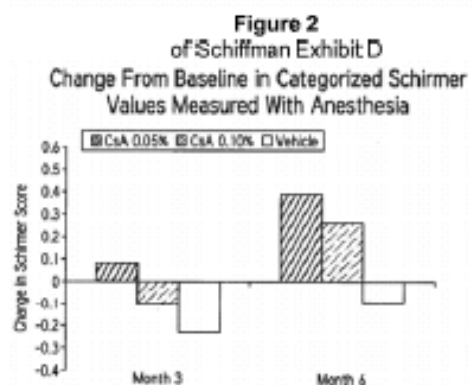
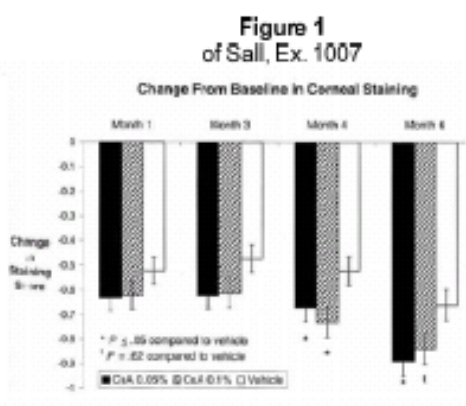
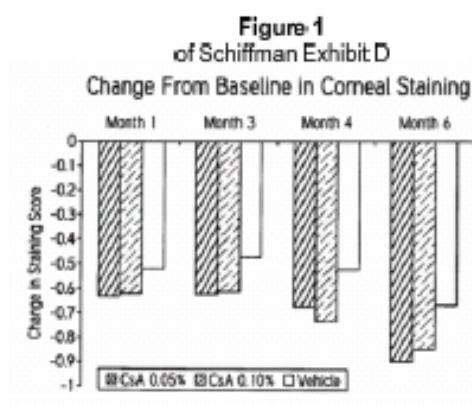
### **A. No Unexpected Results**

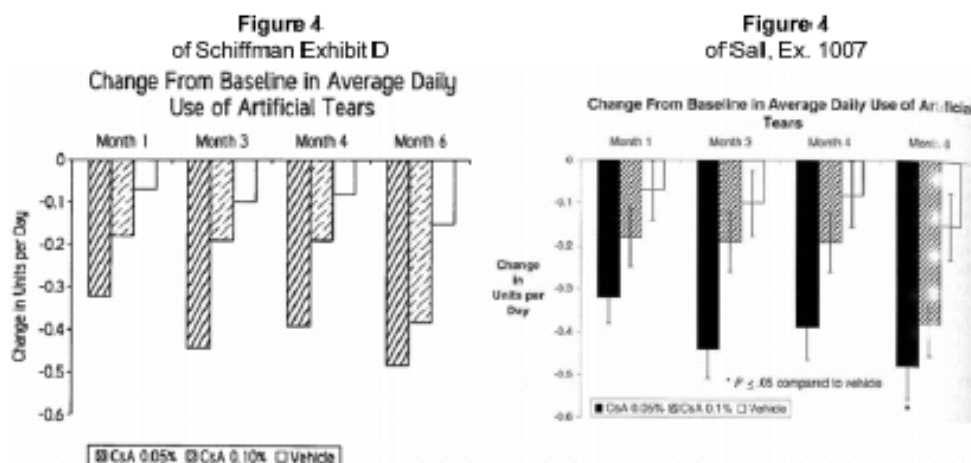
The data provided during prosecution failed to demonstrate unexpected results because it failed to provide parameters necessary for scientific interpretation, including raw data values and error rates. Without these parameters,

it is impossible to reach a scientifically valid conclusion of unexpected results because it is not known whether the reported data are statistically significant or material. EX1002, ¶¶130-33, 140-45 (discussed in further detail below).

Moreover, much of the data relied on as purportedly demonstrating unexpected equivalent efficacy of the 0.05% CsA emulsion and the 0.10% CsA emulsion appear identical to graphs published more than one year before the earliest alleged priority date. EX1002, ¶¶126-27. Results published before the 102(b) bar date cannot properly be deemed “unexpected.” The discussion below uses identifiers from the first Schiffman Declaration because these include the Attar exhibits.

Allergan argued during prosecution that it had changed course regarding the obviousness of the claimed emulsion because, “[s]ince these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims.” EX1004, 0007. However, it appears that Allergan repackaged the previously published graphs from Sall. Figures 1-4 of Schiffman Exhibit D line up squarely with Figures 1-4 of Sall, as exemplified below with side-by-side comparisons of Figures 1-4:





Each of Figures 1-4 of Sall is shown to be comparable to those in Schiffman Exhibit D in the Bhagwat Declaration. EX1002, ¶¶129-32.

According to Schiffman, Figures 1-4 of Schiffman Exhibit D are from Allergan’s Phase 3 trials comparing the efficacy and safety of the 0.10% CsA / 1.25% castor oil emulsion to the 0.05% CsA/ 1.25% castor oil “and to a vehicle containing 1.25% by weight castor oil [Ding ’979 Example 2C].” EX1004, 0247. Dr. Attar similarly references the Phase 3 clinical trial. *Id.* at 0273-74. Drs. Schiffman and Attar appear to be referring to the Phase 3 trials described in Sall. EX1007, 631, 638 (reporting results of Allergan’s “multicenter, randomized, double-masked” Phase 3 clinical trials. EX1002, ¶126.

Consistent with standard scientific practices, Sall presents these data by providing the error bars that are missing from the versions presented in the later Schiffman and Attar declarations. EX1002, ¶129. Though lacking parameters necessary to reach a scientific conclusion, Schiffman interpreted the data as

“surprisingly exhibit[ing] a **comparable** or greater decrease in corneal staining.”

EX1004, 0249 (emphasis added). Sall, however, had previously reported that the decrease in corneal staining and the increase in Schirmer score were comparable between the 0.05% CsA and 0.10% CsA emulsions:

Treatment with CsA, 0.05% or 0.1% gave significantly ( $P \leq 0.05$ ) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values) . . . .

***There was no dose-response effect.*** Both CsA treatments exhibited an excellent safety protocol.

EX1007, 638 (emphasis added); *id.* (“In this study, the most important overall finding was that topical treatment with either CsA 0.05% or 0.1% resulted in significantly greater improvements . . . .”). An assertion that a composition is at least as effective as another composition cannot constitute surprising or unexpected results when the prior art teaches such efficacy. This same analysis applies to Figures 2- 4 of Schiffman Exhibit D. EX1002, ¶132.

Moreover, Stevenson had previously determined that the 0.05% CsA and 0.10% CsA emulsions were the “most appropriate formulations” because no “additional benefits were observed with the higher concentrations.” EX1015 at 967; EX1002, ¶165. At best, Schiffman Exhibit D merely confirms the teachings of the prior art that the 0.05% and 0.10% CsA emulsions had similar results.



Schiffman Exhibits B-C and E-F also fail to establish unexpected results because they again do not provide necessary parameters to permit a scientific conclusion of unexpected results. EX1002, ¶¶130, 132, 133, 139, 144-45. As can be seen in the reproduction below, Exhibit B contains brackets suggesting that the Phase 2 results indicated that the 0.10% CsA emulsion was significantly more effective than the 0.05% CsA emulsion. *Id.* at 0275. Such an interpretation is not supported by Exhibit B, however, for several reasons. EX1002, ¶¶139-43.

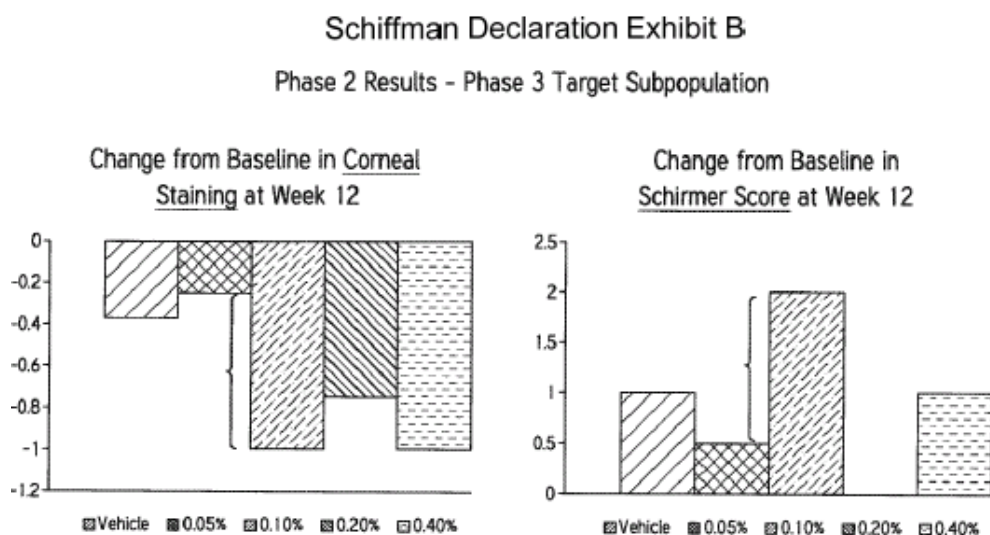


FIG. 1

FIG. 2

For example, Exhibit B lacks error bars. EX1002, ¶¶140-41. Without error bars, it is impossible to determine whether the results shown in Exhibit B are statistically significant. If not statistically significant, the observed results may simply be the result of chance variation due, for example, to sampling error.

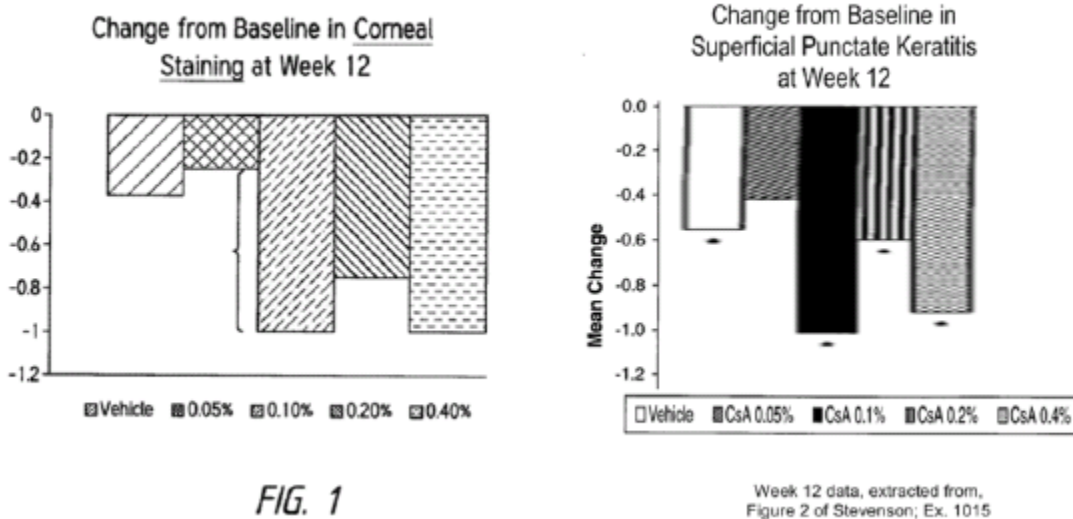
EX1002, ¶¶140-41. Because of the absence of error bars, Dr. Schiffman's assertion, based on Exhibit B, that "the 0.1% by weight cyclosporin A/ 1.25% by weight castor oil formulation demonstrated a greater increase in Schirmer Score (tear production) at week 12 than any other formulation tested," EX1004, 0247 (emphasis in original), lacks support.

In addition to being unsupported, Dr. Schiffman's conclusion may be incorrect. As explained by Dr. Bhagwat, the Stevenson publication reported Phase 2 results of the CsA clinical trial. EX1002, ¶142. Stevenson concluded that CsA emulsions containing 0.05%, 0.10%, 0.20%, and 0.40% CsA all "significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and decreased the effect of the disease on vision-related functioning," and that "Cyclosporin A 0.05% and 0.1% were deemed the most appropriate formulations for future clinical studies because no additional benefits were observed with the higher concentrations." EX1015 at 967; EX1002, ¶142.

With respect to the Schirmer tear tests, Stevenson reports the results of the Schirmer test in the Phase 2 CsA trials "only approached statistical significance" for the 0.10% CsA emulsion. EX1015, at 971. This indicates the change in Schirmer score of 2 units for the 0.10% CsA group in Fig. 2 of Schiffman Exhibit B is not even statistically significantly different from 0 (baseline). EX1002, ¶¶143-44. Thus, the approximately 1.5 unit bracket drawn between the 0.05% and

0.10% CsA groups, even if fully attributable to the difference in CsA%, is also small enough to be statistically insignificant in this study. As explained by Dr. Bhagwat, errors of this size are not unexpected because of the small sample. EX1002, ¶144; EX1015 at 970.

Similarly, regarding Schiffman’s Exhibit B, Figure 1, for the results of the corneal staining tests used to measure Superficial Punctate Keratitis (“SPK”), Stevenson also published a graph of the SPK corneal staining results, which is shown below (right) adjacent to the corneal staining results from Figure 1 of Schiffman Exhibit B (left). EX1002, ¶143. Stevenson stated that “[n]o statistically significant among-group differences in [SPK] were observed.” EX1002, ¶143; EX1015 at 968, 971.



Although some differences exist between the graphs, Stevenson demonstrates how the absence of error bars in Schiffman Exhibit B renders

impossible any valid conclusion as to the significance of the 0.10% CsA emulsion.

Moreover, even if statistically significant, the differences in Phase 2 results between the 0.05% and 0.10% CsA emulsions cited by Dr. Schiffman appear to be immaterial. Despite the apparent gap between the 0.05% and 0.10% CsA emulsions in the Stevenson figure, Stevenson concluded that CsA emulsions “0.05% and 0.1% were *deemed the most appropriate formulations* for future clinical studies because no additional benefits were observed with the higher concentrations.” EX1015, 967; EX1002, ¶142.

Schiffman’s Exhibit C, which addresses the concentration of CsA found in the cornea and conjunctiva tissues following the administration of the claimed emulsion versus one which comprises half as much castor oil, similarly fails to establish any significant or material difference between the tested emulsions. Schiffman Exhibit C again lacks error bars (EX1004, 0263), which prevents any conclusion of statistical significance. EX1002, ¶145. Further, Schiffman Exhibit C fails to establish materiality of any observed differences, even if significant. Well prior to the earliest priority date of the ’111 patent, the minimal concentration of CsA needed in ocular tissues for therapeutic effectiveness was already known. EX1002, ¶145; EX1011, 652. It was also known that topical ophthalmic CsA in castor oil provided therapeutic concentrations, and that 0.05% CsA emulsions in particular were sufficient to “significantly decrease[]” markers associated with dry

eye disease/KCS. EX1002, ¶145; EX1014, 496. Instead of comparing the tissue CsA concentrations measured in Exhibit C to the known threshold for therapeutic efficacy, however, Exhibit C compares them to levels observed with 0.1% CsA/1.25% castor oil. Because Exhibit C reports no raw values, it is impossible to conclude that any observed increase is material. EX1002, ¶145.

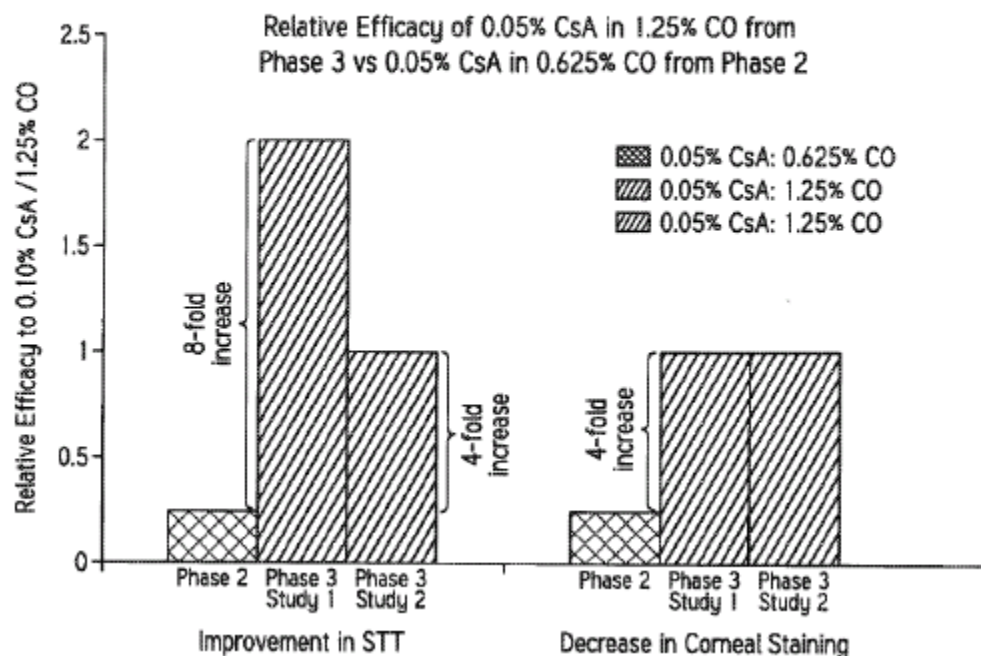
Schiffman Exhibits E and F are a table and a graph of data said to originate from the Phase 2 and Phase 3 trials of Restasis<sup>®</sup>. EX1004, 0237-40. These exhibits allege efficacy of the claimed emulsion (0.05% CsA/1.25% castor oil) relative to two other emulsions: 0.1% CsA/1.25% castor oil (Ding 1D) and 0.05% CsA/0.625% castor oil (Ding 1E). EX1002, ¶133. Schiffman states there was an “8-fold increase” in the performance of the claimed emulsion over Ding ’979’s 1E formulation. Stevenson and Sall, however, reported results of Phase 2 and Phase 3 trials of Restasis<sup>®</sup> respectively, and both reported that variations between emulsions containing 0.05% and 0.10% CsA were not significant. EX1007, 631; EX1015, 967; EX1002, ¶¶ 74, 137, 142-44.

### Schiffman Declaration Exhibit E

	Phase 2 001	Phase 3 (1 <sup>st</sup> study)	Phase 3 (2 <sup>nd</sup> study)
	0.05% CsA in 0.625% CO	0.05% CsA in 1.25% CO	0.05% CsA in 1.25% CO
	Compared with 0.1% CsA in 1.25% CO		
Improvement in STT	0.25	2 (8-Fold Improvement*)	1 (4-Fold Improvement*)
Decrease in Corneal Staining	0.25	1 (4-Fold Improvement*)	1 (4-Fold Improvement*)

\*Compared to the 0.05% CsA/0.625% CO Phase 2 formulation (disclosed in Ding)

### Schiffman Declaration Exhibit F



In contrast to Stevenson's and Sall's reports, Schiffman's analysis is misleading and fraught with scientific inaccuracies. Instead of raw data and error

bars, Exhibits E and F report only “ratios” of the test scores for 0.05% CsA in either 0.625% castor oil or 1.25% castor oil. EX1002, ¶¶133-34. The ratios were purportedly derived by dividing the actual test results for the two 0.05% CsA emulsions by the actual results for the 0.10% CsA / 1.25% castor oil emulsion. However, using ratios instead of raw numbers can exaggerate the importance of very small and immaterial differences. EX1002, ¶¶133-34. Coupled with the failure to report error rates, it is impossible to say that the reported ratio differences are either statistically significant or material. *Id.*

Exhibits E and F indicate that the same Phase 3 study was performed twice. In both, the decrease in corneal staining with the 0.05% CsA/1.25% castor oil emulsion was essentially equivalent to the result with the 0.10% CsA/1.25% castor oil emulsion (reflected in the ratio values of “1” in the corneal staining row of Exhibit E, and as shown graphically in Exhibit F). EX1002, ¶¶133-34. In contrast, the results for the Schirmer Tear Test (STT) varied by as much as 100% across the two Phase 3 studies (reflected in the ratio values of “1” and “2” in the STT row of Exhibit E as reflected graphically in Exhibit F). This suggests a high degree of error in the test and indicates that a difference of “1” in Exhibit E is not statistically significant. It follows that the difference in the STT score of 0.25 and 1 (described in Exhibit E as a 4-fold increase) is not a statistically significant result. EX1002, ¶135. In other words, the difference between a “1” and a “0.25” may simply be

due to chance variation, and there may be no real difference between the two 0.05% CsA emulsions in Exhibits E and F, despite the appearance of a large difference. Further, the fact that the “8-fold Improvement” in STT was not repeatable, and that no 8-fold improvement was observed in corneal staining indicates that this value is unreliable. EX1002, ¶¶136-38.

As such, Exhibits E and F do not demonstrate that increasing the castor oil concentration from 0.625% to 1.25% resulted in any meaningful improvement. Some improvement based on an increase in castor oil would be expected, EX1014, EX1015, and therefore cannot be attributed to an unexpected benefit resulting from the specific CsA concentration and the specific castor oil concentration claimed, EX1002, ¶¶137-38.

#### **B. No Evidence of Commercial Success**

During prosecution, the examiner concluded there was no evidence of commercial success because Allergan failed to establish a nexus between sales and the claims that ultimately issued in the '111 patent. EX1004, 0439-40. “For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention.” *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quotation omitted). Allergan failed to compare the commercial performance of Restasis® to any alternatives because it defined all alternatives out



of the relevant market. EX1004, 0291 (“Restasis<sup>®</sup> owns 100% of the market share”). Further, the required nexus was lacking because the sales were not attributable to using the 0.05% CsA emulsion. “Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.” *In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

In addition, Ding ’979 was listed in the Orange Book for Restasis<sup>®</sup> and thus presumptively blocked the entry of both the claimed emulsion and also comparable emulsions until 2014. EX1024, 0007. Thus, any sales of Restasis<sup>®</sup> that can be attributed to the medication (as opposed to what Allergan conceded was its decade-long marketing efforts (EX1004, 0397) and to the narrow definition of the relevant market) cannot be attributed to the 0.05% CsA emulsion because the 0.10% CsA emulsion was also safe and effective and was as substantially effective as the 0.05% CsA emulsion. For example, the patent itself allegedly teaches the claimed emulsion is as substantially therapeutically effective as the prior art 0.10% CsA/1.25% castor oil emulsion, which is Example 1D of Ding ’979. EX1001, 14:14-44; EX1006, 4:32-43. Sall also taught that the 0.05% CsA emulsion was as substantially therapeutically effective as the 0.10% CsA emulsion. Section VIII, *supra*.

Because Allergan failed to provide legally relevant comparisons and did not permit sales of comparable emulsions, its evidence of sales of Restasis<sup>®</sup> lacks the required nexus to the claimed invention to support patentability.

**C. No Industry Praise**

Dr. Schiffman asserted in his second declaration that “Restasis<sup>®</sup> has been well received by the medical community.” EX1004, at 0303. Allergan cited no industry praise, however, during prosecution that related to the claims of the ’111 patent specifically or that would distinguish the claimed emulsion from the prior art 0.10% CsA emulsion of Ding ’979 Example 1D. *Id.* at 0303, 0393 (referring to the use of topical CsA without differentiating between Restasis<sup>®</sup> and the topical CsA treatment of Ding ’979’s Example 1D). Thus, no nexus was shown to exist between the claims and alleged praise.

**D. No Long-Felt, Unmet Need**

Allergan failed to demonstrate any nexus between the alleged long-felt need and the claims of the ’111 patent. As discussed above, Allergan’s Ding ’979 patent prevented sales of alternative comparable emulsions, including a 0.1% CsA emulsion that was as substantially therapeutically effective as a 0.05% emulsion. Furthermore, topical ophthalmic products were already available for those suffering from dry eye disease/KCS, including GenTeal<sup>®</sup>, Hypotears<sup>®</sup> PF, Moisture Eyes<sup>®</sup>, Refresh<sup>®</sup> Plus, Refresh<sup>®</sup> Tears, Tears Naturale Free<sup>®</sup>, and TheraTears<sup>®</sup>.

EX1020, 0002. There was no long-felt need established, nor a nexus shown between an alleged long-felt need and how it was adequately addressed by the claimed invention.

**E. No Failure of Others**

Dr. Schiffman asserted, “Other companies have tried to develop prescription treatments for dry-eye, but none have been FDA approved as of this date.”

EX1004, at 0304. No evidence of failure on a technical or scientific level was presented, however, and a general assertion without supporting evidence does not demonstrate a failure of others. *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1332 (Fed. Cir. 2009). As the owner of Ding ’979, only Allergan could have obtained FDA approval of Example 1D of Ding ’979. The failure to obtain FDA approval of Example 1D appears to be a self-inflicted failure of Allergan’s own design. Moreover, as discussed above in Section D, other topical ophthalmic products were available for patients suffering from dry-eye diseases. Allergan failed to establish a nexus between the ’111 patent’s claims and any purported failure of others.

**X. ADDITIONAL ARGUMENTS AND/OR REASONING**

**A. Judicial Estoppel**

As noted above, during prosecution of the parent application which successfully issued, Patent Owner admitted that the claimed emulsion “is squarely

within the teaching of the Ding [’979] reference” and “would have been obvious.”

EX1005, 0435; EX1002, ¶18. This adverse admission is binding on Allergan under the doctrine of judicial estoppel. Under the doctrine of judicial estoppel, “where a party successfully urges a particular position in a legal proceeding, it is estopped from taking a contrary position in a subsequent proceeding where its interests have changed.” *Data Gen. Corp. v. Johnson*, 78 F.3d 1556, 1565 (Fed. Cir. 1996). The doctrine applies to agency proceedings. *Id.* (“Although the Board is not a court, we assume it has authority by analogy to apply the doctrine in an appropriate case.” (citing *Reynolds v. Commissioner*, 861 F.2d 469, 472-74 (6th Cir. 1988) (affirming application of doctrine of judicial estoppel by the Tax Court despite its lack of general equitable powers))). Accordingly, Allergan cannot now disclaim its earlier admission of obviousness.

## **B. Later-Discovered Secondary Considerations**

Allergan’s alleged “unexpected results” discussed *supra* further fail to demonstrate patentability because the data were not available to a skilled artisan at the time of invention but only years after Allergan’s earliest admissions were made. The later-discovered data have little-to-no evidentiary value. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 979 (Fed. Cir. 2014) (discounting secondary considerations where “inventors did not know about [the invention’s] hepatitis B properties until four years after the filing date” and

therefore “agree[ing] with the district court that the evidence of long-felt need is of limited value”).

### **C. Additional Legal Support for Anticipation**

Additional legal support for the anticipation ground, *supra*, can be found in *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1382 (Fed. Cir. 2015). There, in reviewing an *inter partes* review decision, the Federal Circuit affirmed the Board’s finding of anticipation based on a prior art patent because, while a claim in the prior art patent recited all but one limitation of the challenged patent claim, the prior art claim had “a specific hook back into the . . . disclosure” that disclosed the one limitation not expressly recited in the prior art claim. *Id.* at 1380. That specific hook, the Federal Circuit concluded, was sufficient for one of skill in the art to immediately envisage the claimed subject matter. *Id.* at 1383. Moreover, “actual performance” of the claimed subject matter was not necessary. *Id.* (citing *Novo Nordisk Pharm., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed. Cir. 2005)). “Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.” *Id.* (quoting *Bristol-Myers Squibb*, 246 F.3d at 1379).”

As in *Kennametal*, a skilled artisan, reading Ding ‘979 would have at once envisaged the CsA/castor oil amounts in the claimed combination, *i.e.*, 0.05% CsA and 1.25% castor oil.

**D. Presumptive Enablement of Ding ‘979**

Further support for the conclusion that Ding ‘979 anticipates and/or renders obvious the challenged claims is that claims of Ding ‘979, *e.g.*, claim 8, cover the same compositions as claimed in the challenged ‘111 patent. Specifically, claim 8 of Ding ‘979 recites : CsA of 0.05-0.4%; castor oil of 0.625-5%; polysorbate 80. Thus, any argument that the prior art Ding ‘979 does not enable what is claimed in the ‘111 patent must be rejected. *See Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (“[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.”).

**E. Ding ‘979 Directs One to the Claimed Emulsion**

Ding ‘979 further directs one of skill in the art to the specific emulsion having 0.05% CsA and 1.25% castor oil. A skilled artisan would start with CsA at 0.05% because that is the concentration at which the therapeutic effect of CsA is maximized. One would then maintain that CsA concentration constant while varying castor oil concentration, guided by Ding ‘979’s teaching that of the “more preferably” preference that the weight ratio of CsA to castor oil is “between 0.12 to 0.02.” Thus, 1.25% castor oil (a weight percent disclosed in several examples) gets you a ratio of 0.04, which is within the preferred range.

**XI. CONCLUSION**

For the above reasons, claims 1-27 of the '111 patent are unpatentable over the asserted prior art. Petitioners therefore request institution of an *inter partes* review and that the claims be canceled.

Respectfully submitted,

Dated: June 22, 2016

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## **XII. CERTIFICATE OF COMPLIANCE**

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,985 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a).

Respectfully,

Dated: June 22, 2016

/Matthew J. Dowd/  
Matthew J. Dowd, Lead Counsel  
Reg. No. 47,534  
*Counsel for Petitioner*



**XIII. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103**

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 50-2849.

**XIV. APPENDIX - LIST OF EXHIBITS**

<b>Exhibit No.</b>	<b>Description</b>
1001	U.S. Patent No. 8,629,111 to Acheampong <i>et al.</i>
1002	Declaration of Dr. Dileep Bhagwat
1003	<i>Curriculum Vitae</i> of Dr. Dileep Bhagwat
1004	File history of U.S. Patent No. 8,629,111 to Acheampong <i>et al.</i>
1005	File history of U.S. Patent Application No. 10/927,857, filed on August 27, 2010 to Acheampong <i>et al.</i>
1006	U.S. Patent No. 5,474,979 to Ding <i>et al.</i> , filed May 17, 1994
1007	K. Sall, <i>et al.</i> , <i>Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease</i> , 107 <i>Ophthalmology</i> 631 (2000)
1008	A. Acheampong <i>et al.</i> , <i>Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, in Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2: Basic Science and Clinical Relevance</i> 1001 (ed. David A. Sullivan & Darlene A. Dartt 1998)
1009	U.S. Patent No. 5,578,586 to Glonek <i>et al.</i> , filed February 4, 1994
1010	U.S. Patent No. 5,981,607 to Ding <i>et al.</i> , filed January 20, 1998

1011	R. Kaswan, <i>Intraocular Penetration of Topically Applied Cyclosporine</i> 20 Transplantation Proceedings 650 (1988)
1012	K. Kunert <i>et al.</i> , <i>Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome</i> , 118 Archives of Ophthalmology 1489 (2000)
1013	Physicians' Desk Reference for Ophthalmic Medicines (1999)
1014	K. Turner <i>et al.</i> , <i>Interleukin-6 Levels in the Conjunctival Epithelium of Patients with Dry Eye Disease Treated with Cyclosporine Ophthalmic Emulsion</i> 19 Cornea 492 (2000)
1015	D. Stevenson <i>et al.</i> <i>Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease</i> 107 Ophthalmology 967 (2000)
1016	Gerald Hecht, <i>Ophthalmic Preparations</i> , in <i>Remington: The Science And Practice Of Pharmacy</i> 821(A. Gennaro ed. 2003)
1017	E. Goto <i>et al.</i> <i>Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction</i> 109 Ophthalmology 2030 (2002)
1018	A. Kanpolat <i>et al.</i> , <i>Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration</i> 20 CLAO J. 119 (1994)
1019	A. Vieira <i>et al.</i> , <i>Effect of ricinoleic acid in acute and subchronic experimental models of inflammation</i> , 9 Mediators of Inflammation 223 (2000)

1020	R. Murphy, <i>The Once and Future Treatment of Dry Eye</i> , Review of Optometry 1 (2000)
1021	D. Small <i>et al.</i> , <i>Blood Concentrations of Cyclosporin A During Long-Term Treatment with Cyclosporin A Ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease</i> 18 J. Ocular Pharmacology & Therapeutics 411 (2002)
1022	Stedman's Medical Dictionary 27 <sup>th</sup> Edition (M.B. Pugh ed. 2000)
1023	Complaint; <i>Allergan, Inc. v. Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Apotex, Inc., Apotex Corp., Akorn, Inc., Mylan Pharmaceuticals Inc., and Mylan Inc.</i> , No. 2:15-cv-01455
1024	Approved Drug Products with Therapeutic Equivalence Evaluations (34th Ed.) (2014) (Excerpts)
1025	Complaint; <i>Allergan, Inc., v. Innopharma, Inc. and Pfizer, Inc.</i> , No. 2:15cv1504
1026	Complaint, <i>Allergan, Inc. v. Famy Care Ltd.</i> , No. 16-00401 (E.D. Tex. filed Apr. 12, 2016)

**CERTIFICATE OF SERVICE**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *inter partes* review of U.S. Patent No. 8,629,111 (and accompanying Exhibits 1001-1026) by overnight courier (Federal Express or UPS), on this 22nd day of June, 2016, on the Patent Owner at the correspondence address of the Patent Owner as follows:

ALLERGAN, INC.  
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Irvine, CA 92612-1599

and at other addresses also likely to effect service:

Dorothy P. Whelan  
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Respectfully,

Dated: June 22, 2016

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