

Filed on behalf of Akorn Inc.
By: Michael R. Dzwonczyk
Azy S. Kokabi
Sughrue Mion, PLLC
2100 Pennsylvania Ave., NW
Washington, DC 20037
Telephone: 202-293-7060
Facsimile: 202-293-7860
email: mdzwonczyk@sughrue.com
akokabi@sughrue.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AKORN INC.
Petitioner

v.

ALLERGAN, INC.
Patent Owner

Case No. IPR2017-00599
Patent No. 8,633,162

DECLARATION OF MANSOOR AMIJI, PH.D.

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I, Mansoor Amiji, declare as follows:

I. QUALIFICATIONS

1. My name is Mansoor Amiji. I am currently the Bouvé College Distinguished Professor in the Department of Pharmaceutical Sciences in the School of Pharmacy at Northeastern University. I have been a member of the faculty at Northeastern since 1993. I am also an affiliate faculty member in the Departments of Chemical Engineering and Biomedical Engineering within the College of Engineering at Northeastern, as well as a Distinguished Adjunct Professor within the Faculty of Pharmacy at King Abdulaziz University.

2. I received a B.S. in Pharmacy from Northeastern University in 1988, and a Ph.D. in Pharmaceutics/Biomaterials Science from Purdue University in 1992. I have also conducted research as a Senior Research Scientist at the Columbia Research Laboratories in Madison, Wisconsin, as well as served as a Visiting Research Scholar in the Department of Chemical Engineering at MIT.

3. My current research focuses on the development of biocompatible materials from natural and synthetic polymers, target-specific drug and gene delivery systems for cancer and infectious diseases, and nanotechnology applications for medical diagnosis, imaging and therapy. I have extensive experience with pharmaceutical formulations, including oil-in-water emulsions containing various types of oils, including castor oil, as well as with sterile formulations and dosage forms for use in the eye. I have also taught courses on the development and characterization of ophthalmic formulations to undergraduate pharmacy and graduate students.

4. I have had extensive experience in the development and characterization of lipid-based drug delivery systems, including oil-in-water emulsion formulations intended for parenteral and oral administration. I have also worked on emulsion formulations that are targeted to different parts of the body, including the brain.

5. My research has been funded by such organizations as the National Institute of Health (NIH) and the National Science Foundation (NSF), as well as other government agencies and foundations. I also serve, or have served, on the editorial board of thirteen peer-reviewed journals such as *Drug Design: Development and Therapy*, *Expert Opinion on Drug Delivery*, *Pharmaceutical Formulations and Quality*, and *Tissue Barriers*. I have also served as a reviewer for 39 peer-reviewed journals including *Science*, *Angewandte Chemie International Edition*, *European Journal of Pharmaceutical Sciences*, *Journal of Pharmaceutical Sciences*, and *Nature Communications*.

6. I have authored or co-authored more than 200 peer-reviewed journal articles. I have also authored 43 book chapters and been listed as an inventor on 16 patents and patent applications. I have given over 170 invited seminars at scientific symposia and educational institutions.

7. I have received numerous honors and awards, including my 2014 induction into the College of Fellows at the Controlled Release Society, appointment as an Honorary Member in the Phi Lambda Sigma Pharmacy Leadership Society, a fellowship as well as the Meritorious Manuscript Award

from the American Association of Pharmaceutical Sciences, and the Eurand Award for Outstanding Research in Oral Drug Delivery.

8. A summary of my education, experience, publications, awards and honors, patents, publications, and presentations is provided in my CV, a copy of which is submitted separately. Ex. 1003.

II. SCOPE OF WORK

9. I understand that a petition is being filed with the United States Patent and Trademark Office for *Inter Partes* Review of U.S. Patent No. 8,633,162 (“the ’162 patent,” Ex. 1001). I have been retained by the Petitioner as a technical expert to provide analysis and opinions regarding the ’162 patent. I have reviewed the ’162 patent and relevant sections of its prosecution history in the United States Patent and Trademark Office. Ex. 1004. I have also reviewed and considered various other documents in arriving at my opinions, and cite them in this declaration. For convenience, documents cited in this declaration are listed in the Appendix in Section XII.

10. I am compensated at the rate of \$870/hour for my work. I have no financial interest in the outcome of this matter.

III. OVERVIEW OF THE ’162 PATENT

11. The ’162 patent issued January 21, 2014. The ’162 patent is entitled “Methods of Providing Therapeutic Effects using Cyclosporin Components.” The first page of the patent states that an application for the ’162 patent (U.S. Application No. 13/967,179, “the ’179 application”) was filed on August 14, 2013 and claims priority through a series of continuations to U.S. Application No.

10/927,857 (“the ’857 application,” Ex. 1005), and thereby to U.S. Provisional Patent Application No. 60/503,137, filed on September 15, 2003.

12. The ’162 patent is generally directed to methods of treatment of ocular disorders using pharmaceutical compositions of cyclosporin A (referred to herein as “CsA”). Claim 1 of the ’162 patent recites the following:

1. A method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective at treating dry eye disease.

Ex. 1001, col. 15, ll. 22-30.

13. Claim 2 depends from claim 1 and recites that the emulsion further comprises a tonicity agent or a demulcent component. Claim 3 further depends from claim 2, and recites that the tonicity agent or demulcent component is glycerine. Claim 4 depends from claim 1, reciting that the emulsion further comprises a buffer; claim 5 further depends from claim 4, and recites that the buffer is sodium hydroxide. Claims 6-9 also depend from claim 1, reciting that the topical ophthalmic emulsion further comprises glycerine and a buffer, that the emulsion comprises polysorbate 80 in an amount of 1.0% by weight, that the emulsion comprises acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight, and that the emulsion further comprises glycerine in an amount of 2.2% by weight and a buffer, respectively. Claim 10 depends from

claim 9, reciting that the buffer is sodium hydroxide. Percent values refer to % by weight throughout this declaration unless otherwise indicated.

14. Claim 11 depends from claim 1, and recites that when the emulsion is topically administered to the human eye, “the blood of the human has substantially no detectable concentration of cyclosporin A.” *Id.* at col. 15, ll. 51-53. Claim 12 depends from claim 6, reciting that the emulsion has a pH in the range of about 7.2 to about 7.6. Claims 13 and 14 depend from claim 1, reciting that the emulsion is “as substantially therapeutically effective as” and “achieves at least as much therapeutic effectiveness as,” a similar emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight. *Id.* at col. 15, l. 56 – col. 16, l. 4. Similarly, claim 15 depends from claim 1, reciting that the emulsion breaks down more quickly in the eye of a human, “thereby reducing vision distortion” as compared to a second emulsion that contains only 50% as much castor oil. *Id.* at col. 16, ll. 5-9. Claim 16 depends from claim 1, reciting that the emulsion, when administered to the human eye, demonstrates “a reduction in adverse events” as compared to a second emulsion comprising 0.1% by weight cyclosporin A and 1.25% castor oil. *Id.* at col. 16, ll. 10-17. Claim 17 further depends from claim 16, reciting that the adverse events are side effects.

15. Claim 18 of the '162 patent is an independent claim to a method of treatment, and recites the following:

18. A method of reducing side effects in a human being treated for dry eye syndrome, the method comprising the step of

topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises:

cyclosporin A in an amount of about 0.05% by weight;

castor oil in an amount of 1.25% by weight;

polysorbate 80 in an amount of about 1.0% by weight;

acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;

a tonicity component or a demulcent component in an amount of about 2.2% by weight;

a buffer; and

water;

wherein the topical ophthalmic emulsion has a pH in the range of about 7.2 to about 7.6.

Id. at col. 16, ll. 20-36.

16. Claims 19-22 depend from claim 18, and recite that the buffer is sodium hydroxide, the tonicity/demulcent component is glycerine, that “when the emulsion is administered to the eye of a human for treating dry eye syndrome, the blood of the human has substantially no detectable concentration of the cyclosporin A,” and that the emulsion is effective in treating dry eye disease. *Id.* at col. 16, ll. 37-46.

17. Claim 23 of the '162 patent is an independent claim to a method for the treatment of keratoconjunctivitis sicca, and recites the following:

23. A method of treating dry eye disease, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion at a frequency of twice a day, the emulsion comprising:

cyclosporin A in an amount of about 0.05% by weight;
castor oil in an amount of about 1.25% by weight;
polysorbate 80 in an amount of about 1.0% by weight;
acrylate/C10-30 alkyl acrylate cross-polymer in an amount of about 0.05% by weight;
glycerine in an amount of about 2.2% by weight;
sodium hydroxide; and
water; and
wherein the emulsion is effective in treating dry eye disease.

Id. at col. 16, ll. 47-60.

Finally, claim 24 depends from claim 23, reciting that the emulsion has a pH in the range of about 7.2 to about 7.6.

IV. FILE HISTORY OF THE '162 PATENT

18. As noted above, the instant patent that issued from the '179 application resulted from continuations of the '857 application. During prosecution of the '857 application, the applicant expressly admitted that the emulsion, referred to as Composition II, and which remains the emulsion recited in the method of treatment claims in the '162 patent, was squarely within the teachings of U.S. Patent No. 5,474,979 (filed May 17, 1994) to Ding *et al.* ("Ding '979," Ex. 1006). The applicant stated:

The applicants concede that it would have been obvious to modify examples 1A-1E of the Ding ['979] reference to arrive at Composition II of the present application. The differences are insignificant. One need only use the cyclosporin concentration of Example 1E (0.05%), the castor oil concentration of Example 1D (1.250%), and the remaining ingredients of those examples. 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 ['979] reference, and the Office should disregard any statements by the applicants suggesting otherwise[.]

Ex. 1005 at 0435.

As discussed below, I agree with these statements.

19. I have reviewed the content of the '857 application concurrently with that of the '162 patent and find Composition II of the '857 application to be indistinguishable from the emulsion claimed in the '162 patent. A table submitted by the applicant during prosecution of the '857 application has been included below, and extended to include the emulsion of the '162 patent for convenient comparison.

Compositions of the Ding reference compared to

Composition II of the present application

	Ding <i>et al.</i> Example 1B	Ding <i>et al.</i> Example 1D	Ding <i>et al.</i> Example 1E	Composition II ('857 Application)	Composition of the '162 Patent Claims
Cyclosporin A	0.20 %	0.10 %	0.05 %	0.05 %	0.05 %
Castor Oil	5.00 %	1.250 %	0.625 %	1.250 %	1.250 %
Polysorbate 80	1.00 %	1.00 %	1.00 %	1.00 %	1.00 %
Pemulin®	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
cyclosporin : castor oil	0.04	0.08	0.08	0.04	0.04

Ex. 1005 at 0434 (right-most column added). The '857 application was ultimately abandoned. Ex. 1004 at 0002.

20. As mentioned above, the '179 application resulted from a series of continuations from the abandoned '857 application. *Id.* During prosecution of the '179 application, the applicants acknowledged their prior admissions, stating that they had been collecting evidence to support the patentability of the claims “[s]ince these comments have been filed.” Ex. 1004 at 0007. The examiner thereafter rejected the claims under 35 U.S.C. § 103 as being obvious over Ding '979 and for double patenting over Ding '979. *Id.* at 0126-43.

21. On October 3, 2013, the examiner conducted an interview with four representatives of applicants. *Id.* at 0194. According to the applicants' interview summary, the applicants presented “Data demonstrating unexpected results and commercial success of the claimed method” and “Data and information regarding

the claimed method's satisfaction of a long-felt need." *Id.* Applicants' principal argument was that "the evidence of non-obviousness presented at the interview overcomes the *prima facie* obviousness rejection." *Id.*

22. On October 14, 2013, the applicants amended the claims to, among other things, substitute the generic term "acrylate/C10-30 alkyl acrylate cross-polymer" for the trade name Pemulen[®] and substitute the full term "keratoconjunctivitis sicca" for the acronym "KCS." *Id.* at 0189-93. The applicants stated without elaboration that "the *prima facie* case of obviousness has not been properly established against the pending claims," but based their argument on their assertion that "the unexpected results, commercial success, and satisfaction of long felt need obtained with the claimed methods and the failure of others overcome the *prima facie* obviousness rejection asserted in the Office Action." *Id.* at 0195. The applicants submitted four declarations in support of their assertions: two by Rhett Schiffman, one by Mayassa Attar, and one by Aziz Mottiwala. Specifically, applicants argued, based on one Schiffman declaration ("Schiffman Declaration 1") and the Attar Declaration that "**there are new and unexpected results relative to the prior art.**" *Id.* at 0196 (emphasis in original). The applicants relied on "unexpected results compared to the prior art" in Schirmer Tear Testing and decreased corneal staining, as well as reduction of blurred vision and decreased use of artificial tears. *Id.* I discuss Schiffman Declaration 1, as well as the Attar declaration, in Section X below.

23. The examiner issued a Notice of Allowance on December 6, 2013. *Id.* at 0393. The examiner concluded that applicants had failed to demonstrate

commercial success or long-felt need. *Id.* at 0403-05. However, relying on Schiffman Declaration 1 and the Attar Declaration, the examiner concluded 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 keratoconjunctivitis sicca,” and therefore, “demonstrate[s] surprising and unexpected results.” *Id.* at 0407.

24. As set forth in detail throughout this declaration, I disagree with the opinions of Dr. Schiffman and Dr. Attar that the results in the submitted declarations were unexpected or surprising.

V. LEGAL STANDARDS

25. I understand that a claim is not patentable under 35 U.S.C. § 102, for lack of novelty, if each and every element of the claim is described, either expressly or inherently, in a single prior art reference.

26. I have been informed that a claimed invention is not patentable under 35 U.S.C. § 103, for obviousness, if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to “a person having ordinary skill in the art” to which the subject matter of the invention pertains. I understand that “a person of ordinary skill in the art” is a hypothetical person who is presumed to have known the relevant art at the time of the invention. As discussed above, I understand that prior art for the purpose of this declaration includes references that were published at least before September 15, 2003.

27. I have been instructed that, a determination of obviousness requires inquiries into (i) the scope and content of the art when the invention was made; (ii) the differences between the art and the claims at issue; (iii) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, any secondary considerations.

28. I understand that a claim can be found to be obvious if all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable and expected results to one of ordinary skill in the art.

29. I understand that improper hindsight must not be used when comparing the prior art to the invention for obviousness. Thus, a conclusion of obviousness must be firmly based on the knowledge and skill of a person of ordinary skill in the art at the time the invention was made.

30. I have been informed that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the patented invention. I understand that obviousness may be demonstrated by showing that it would have been obvious to combine the teachings of more than one item of prior art. I understand that in order for a combination of references or teachings to render the claimed invention obvious, there must be some supporting rationale for combining the cited references or teachings as proposed.

31. I am informed that the following are examples of principles that may indicate that it would have been obvious to combine multiple teachings, resulting in the claimed combination, if the claimed combination involves: (i) the combination of prior art elements according to known methods to yield predictable results; (ii) the simple substitution of one known element for another to obtain predictable results; (iii) the use of a known technique to improve similar methods or products in the same way; (iv) the application of a known technique to a known method or product ready for improvement to yield predictable results; (v) the application of a technique or approach that would have been “obvious to try” (*e.g.*, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success); (vi) predictable variations of a known work in one field of endeavor prompted for use in either the same field or a different field based on design incentives or other market forces; or (vii) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

32. I also understand that “secondary considerations” may be weighed against evidence of obviousness where appropriate.

33. I understand that such secondary considerations, where in evidence, may include: (i) commercial success of a product due to the merits of the claimed invention; (ii) a long-felt, but unsatisfied need for the invention; (iii) failure of others to find the solution provided by the claimed invention; (iv) deliberate copying of the invention by others; (v) unexpected results achieved by the

invention; (vi) praise of the invention by others skilled in the art; (vii) lack of independent simultaneous invention within a comparatively short space of time; and (viii) teaching away from the invention in the prior art. Secondary considerations are relevant where there is a nexus between the evidence and the claimed invention.

VI. LEVEL OF ORDINARY SKILL AND RELEVANT TIME

34. I have been advised that “a person of ordinary skill in the relevant field” is a hypothetical person who is presumed to have known the relevant art at the time of the invention. A person of ordinary skill in the art is also a person of ordinary creativity. I understand that the relevant timeframe for assessing the validity of claims of the ’162 patent for the purposes of this declaration is assumed to be September 15, 2003, the earliest alleged priority date of the application that led to the ’162 patent. Unless otherwise specifically noted, all of my opinions expressed herein regarding a person of ordinary skill in the art apply to a person of ordinary skill in the art as of September 15, 2003.

35. By virtue of my education, experience, and training, I am familiar with the level of skill in the art of the ’162 patent prior to September 15, 2003. In my opinion, a person of ordinary skill in the relevant field as of September 15, 2003 would typically 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 could have less education but considerable professional experience in one or more of these fields. Additionally, a person of ordinary skill in the art would have been aware of the

information known in the art relating to dry eye/KCS, its causes and known, useful treatments, whether palliative or therapeutic.

36. In particular, one of ordinary skill in the art would likely have some combination of the following skills and experience: (i) experience formulating pharmaceutical products; (ii) experience designing and preparing drug formulations intended for topical ocular administration; (iii) the ability to understand results and findings presented or published by others in the field, including the publications discussed in this declaration.

VII. CLAIM CONSTRUCTION

37. I have been advised that, in the present proceeding, the '162 patent claims are to be given their broadest reasonable interpretation in view of the specification. I also understand that, absent some reason to the contrary, claim terms are typically given their ordinary and accustomed meaning as would be understood by one of ordinary skill in the art. I have followed these principles in my analysis throughout this declaration. The '162 patent provides definitions for certain claim terms. In my opinion, these definitions are conventional. Certain claim terms are not defined in the '162 patent. I discuss a few terms below and what I understand as constructions of these terms.

38. Claims 4-6, 9, 10, 18, and 19 recite that the emulsion of the claimed method comprises a "buffer," while claims 5, 10, and 19 recite that "the buffer is sodium hydroxide." As discussed in the specification, "[t]he pH of the emulsions can be adjusted in a conventional manner using sodium hydroxide . . . to a physiological pH level." Ex. 1001, col. 12, ll. 25-27. The specification also notes

that “suitable buffer components, for example, and without limitation, phosphates, citrates, acetates, borates and the like and mixtures thereof, may be employed to maintain a suitable pH.” *Id.* at col. 12, ll. 32-35. Based on the specification of the ’162 patent, a person of ordinary skill in the art would understand the term “buffer” to include “sodium hydroxide.”

39. Claims 11 and 21 recite that following administration of the claimed emulsion, “the blood of a human has substantially no detectable concentration of the cyclosporin A.” According to the specification: “Cyclosporin component concentration in blood preferably is determined using a liquid chromatography-mass spectroscopy-mass spectroscopy (LC-MS/MS), which test has a cyclosporin component detection limit of 0.1 ng/ml. Cyclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.” Ex. 1001, col. 5, l. 64 – col. 6, l. 3. Notably, neither the claims nor the specification discuss the time point at which the blood levels of CsA are measured. A person of ordinary skill in the art could measure blood concentration at either peak or trough levels, *e.g.*, taking blood samples at serial time points, and determining the maximal concentration, or by taking and testing a blood sample just prior to a second administration of the drug to determine the trough level of the drug in the blood. Taking the broadest reasonable construction for the purposes of this proceeding, the phrase “substantially no detectable concentration” of CsA includes CsA blood levels measured at a concentration below 0.1 ng/mL taken at either peak or trough levels.

40. Independent claims 1 and 23 state that the emulsion is “effective in treating dry eye disease.” Dependent claim 22 recites that the emulsion of independent claim 18 is also “effective in treating dry eye disease.” The ’162 patent identifies that cyclosporin “acts to enhance or restore lacrimal gland tearing in providing the desired therapeutic effect.” Ex. 1001, col. 9, ll. 14-17. During prosecution, the applicants relied on an increase in tearing as demonstrated by the Schirmer Tear Test to assert unexpected efficacy of the claimed emulsion for treating dry eye disease/KCS. *See, e.g.*, Ex. 1004 at 0200 (arguing that the claimed method was “therapeutically effective for the treatment of dry eye or keratoconjunctivitis sicca . . . according to corneal staining score, Schirmer score,” and other measures). In light of the discussion above and in the context of the specification of the ’162 patent, I understand that an emulsion effective in increasing tear production is an example of an emulsion effective in treating dry eye disease/KCS.

41. Dependent claims 13 and 14 respectively describe the emulsion as being “as substantially therapeutically effective as” and having “at least as much therapeutic effectiveness as” a second emulsion with 0.10% CsA and 1.25% castor oil. The word “therapeutic” means “[r]elating to . . . the treatment, remediating, or curing of a disorder or disease.” Ex. 1022 at 0007. This includes palliative treatments, which focus on remediation of a disease—*i.e.*, they alleviate the symptoms of the disease. *Id.* at 0004-05. This comports with what the art recognized as a treatment for dry eye disease/KCS. *See Medications for Dry Eye* (1999) In PHYSICIANS’ DESK REFERENCE FOR OPHTHALMOLOGY (27th ed.)

Montvale, NJ: PDR Network (“Ophthalmic PDR,” Ex. 1013) at 13 (“Dry eye is treated with artificial tear preparations and ophthalmic lubricants.”) A person of ordinary skill in the art would not understand the phrases “therapeutically effective” or “therapeutic effectiveness” to be limited to treatment of an immune-mediated response sometimes contributing to the condition.

42. Claims 13 and 14 each depend from claim 1, and therefore a person of ordinary skill in the art would understand the phrases “as substantially therapeutically effective as” and “at least as much therapeutic effectiveness as” to refer back to the efficacy recited in claim 1, “effective in treating dry eye disease.” Accordingly, the plain meanings of these terms include “as substantially therapeutically effective in increasing tear production as” and “at least as much therapeutic effectiveness in increasing tear production as.”

43. Claims 16 and 17 respectively recite that the emulsion of the claimed method has fewer “adverse events” relative to a second emulsion, and that the “adverse events” are “side effects.” The specification further refers to adverse events as “e.g. side effects, drug interactions and the like.” Ex. 1001, col. 15, ll. 9-16. The plain meaning of the phrase “side effects” is “A result of a drug or other therapy in addition to or in extension of the desired therapeutic effect; usually but not necessarily, denoting an undesired effect.” Ex. 1022 at 0006. Accordingly, I understand “adverse events” to include undesirable side effects as well as other negative reactions to the drug. In the context of an agent topically administered to the eye, undesirable side effects commonly include burning, stinging, and general eye pain. *See* Ex. 1007 at 636, Table 3.

44. The specification also gives an example of side effects “which may result from the presence of the cyclosporin component in the blood of the human or animal being treated.” *Id.* at col. 4, ll. 64-66. The ’162 patent also teaches “[o]ne of the important advantages of the present invention is the reduced concentration of the cyclosporin component in the blood of the human or animal,” and that “[o]ne very useful embodiment of the present administering step provides no substantial detectable concentration of cyclosporin component in the blood.” *Id.* at col. 5, ll. 58-60. A person of ordinary skill in the art would understand that the subset of side effects in the context of the ’162 patent “which may result in the presence of the cyclosporin component in the blood” do not occur when there is no substantial detectable concentration of cyclosporin component in the blood.

45. Claim 15 recites that the first emulsion “breaks down” more quickly in the eye of a human as compared to a second emulsion containing only 50% as much castor oil. The ’162 patent states that “a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition.” Ex. 1001, col. 2, ll. 43-49. In the context of an agent topically administered to the eye, the term “breaks down” means that the emulsion differentiates into separate aqueous and oil layers on the eye.

46. I have followed these definitions in my analysis throughout this declaration.

VIII. THE STATE OF THE ART

47. Below I describe some of the relevant aspects of what was generally known in the art as of September 15, 2003.

48. CsA, a well-known immunosuppressant, has been utilized for decades in the treatment of inflammatory diseases such as psoriasis and rheumatoid arthritis, as well as in the prevention of transplant rejection. K. Kunert *et al.*, *Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome* 118 ARCH. OPHTHALMOL. 1489 (2000) (“Kunert,” Ex. 1012). In the 1990’s, CsA was administered topically for the treatment of dry eye disease/KCS, “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 keratoconjunctivitis sicca [KCS].” Ex. 1013 at 13. Regarding CsA-based ophthalmic preparations, Kunert teaches: “Topical CsA has been used as treatment of ocular conditions such as vernal keratoconjunctivitis, corneal transplants, corneal ulcers, and herpetic stromal keratitis.” Ex. 1012 at 1490. Kunert further teaches, “Clinical trials with this drug have shown improvement in various objective measures of KCS such as corneal staining and Schirmer test values.” *Id.*

49. These clinical trials evaluated the efficacy and safety of various CsA emulsions by measuring changes in the levels of inflammatory markers in patients’ eyes (*e.g.* cytokines) and objective clinical criteria for diagnosis of moderate-to-severe KCS (*e.g.* Schirmer tear test and corneal staining). Ex. 1012; *see also*, 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 (2000) (“Turner,” Ex. 1014); D. Stevenson *et al.*, *Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry Eye Disease* 107 OPTHALMOL. 967 (2000) (“Stevenson,” Ex. 1015). From these trials it was established that the maximal therapeutic effect for the topical treatment of dry eye disease/KCS was obtained at 0.05% and 0.10% CsA. Ex. 1015 at 967.

50. As the efficacy of CsA for the treatment of dry eye disease/KCS had been established prior to September 15, 2003, CsA-based pharmaceuticals were prescribed for ophthalmic administration. Ex. 1013 at 18. As described in the “Cyclosporine” section of the PDR for Ophthalmology: “This potent immunosuppressant has a high degree of selectivity for T lymphocytes. Available under the trade name Sandimmune, it has been used in a 2% topical solution as prophylaxis against rejection in high-risk, penetrating keratoplasty and for the treatment of severe vernal conjunctivitis resistant to more conventional therapy, ligneous conjunctivitis unresponsive to other topical therapy, and noninfectious peripheral ulcerative keratitis associated with systemic autoimmune disorders.” Ex. 1013 at 18. Thus, a 2% CsA solution was available and readily prescribed by doctors as a topical treatment of various inflammation-based ophthalmic syndromes.

51. It was well known before the earliest alleged priority date of the patent that castor oil was an effective vehicle for the ophthalmic delivery of CsA for the treatment of dry eye disease/KCS. CsA is a highly lipophilic and non-polar drug that requires formulation to allow it to reach the aqueous environment of the

eye while remaining dissolved in solution. *See* U.S. Patent No. 5,981,607 to Ding *et al.*, filed January 20, 1998 (“Ding ’607,” Ex. 1010) at col. 5, ll. 55-63. It was known in the art that CsA could be safely and effectively supplied and that the solubility issues just described could be addressed by formulating CsA as an oil-in-water emulsion. *Id.* These oil-in-water emulsions were known to offer the advantage of being able to deliver a poorly water-soluble drug in a solubilized form as an eye drop. *Id.*, *see also*, REMINGTON’S 20TH EDITION: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro ed. 2000) (“Remington’s,” Ex. 1016); E. Goto *et al.* *Low-Concentration Homogenized Castor Oil Eye Drops for Noninflamed Obstructive Meibomian Gland Dysfunction* 109 OPTHALMOL. 2030 (2002) (“Goto,” Ex. 1017); *see also*, Ex. 1010. Ding ’607 specifically teaches castor oil as an appropriate vehicle for the topical ophthalmic delivery of lipophilic molecules which are poorly soluble in water, which may be emulsified with water using a nonionic surfactant, such as polysorbate 80. Ex. 1010, col. 5, ll. 55-63.

52. It was well established in the art that in order to be therapeutically effective, “[t]issue concentrations 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 TRANSPL. PROC. 650 (1988) (“Kaswan,” Ex. 1011) at 652. While Kaswan reported CsA tissue concentrations well in excess of these therapeutic values following the topical administration of CsA in olive oil emulsions, it was additionally known in the art 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 (1994) (“Kanpolat,” Ex. 1018) at 121. Turner further taught that 0.05% CsA in castor oil emulsions were effective in reducing inflammatory markers in patients suffering from dry eye disease/KCS. Ex. 1014 (Turner) at 496 (“The most important finding of the present study was that normalized IL-6 levels significantly decreased from baseline after 6 months of treatment with 0.05% CsA.”). Thus, it was known that topical application of CsA-castor oil emulsions, including emulsions comprising 0.05% CsA resulted in tissue CsA levels sufficient for therapeutic efficacy.

53. However, it was also known that CsA percentage in castor oil emulsions could be optimized to maintain efficacy while minimizing the potential for adverse events. For example, it was known that blood CsA concentrations in the range of 75 ng/mL to 655 ng/mL were sufficient to cause “potent immunosuppressant” systemic effects, and that topical ophthalmic emulsions required a 2600-fold lower dosage of CsA than systemic treatment. D. 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. OC. PHARM. THERAP. 411 (2002) (“Small,” Ex. 1021) at 412. In Small, CsA blood concentrations were monitored for six months while patients received topical ophthalmic emulsions containing 0.05% CsA, and “[n]o patient receiving 0.05% CsA had any quantifiable CsA in the blood.” Ex. 1021 at 411. Small taught that “Phase 2 and Phase 3 clinical trials have established both the safety and efficacy of topical CsA [for treating KCS] at concentrations ranging

from 0.05% to 0.4%.” *Id.* at 412. Thus, percentages of CsA as low as 0.05% administered ophthalmically were known in the art to result in undetectable levels of CsA in the blood stream, thereby minimizing the potential for unwanted systemic immunosuppressant effects, while still being efficacious for the treatment of KCS.

54. In addition to providing an effective vehicle for the delivery of CsA, castor oil itself also provided relief to those suffering from dry eye diseases such as keratoconjunctivitis sicca. For example, Ding ’607 is directed to emulsions of a castor oil-based pharmaceutical composition for the alleviation of the symptoms of patients with KCS or dry eye disease. Ex. 1010. Ding ’607 notes that these compositions, “result[] in an emulsion with a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues as well as being suitable itself for alleviating dry eye symptoms.” Ex. 1010, col. 3, ll. 34-38.

55. Ding ’607 also describes one mechanism by which castor oil (made up mostly of higher-order fatty acids, such as the 18-carbon ricinoleic acid) alleviates dry eye/KCS symptoms: “Most importantly, the emulsion of the present invention provides for long retention of the higher fatty acid glyceride [*e.g.*, 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.” *Id.* at col. 3, l. 66 – col. 4, l. 3. Ding ’607 further teaches that a higher concentration of castor oil yields a higher mean ocular residence time, providing improved relief. *See* Figure 7, Ex.

1010. Ding '607 also teaches that the castor oil emulsion “increases the measured tear volume,” as measured by a Schirmer tear test. *Id.* at col. 6, ll. 49-63.

56. Similar findings of the effect of castor oil on KCS were reported in other clinical trials. For example, Turner refers to a “large therapeutic effect” of the castor oil vehicle, which had been utilized as a control treatment for evaluating the efficacy of CsA/castor oil emulsions for the treatment of dry eye/KCS. Ex. 1014 at 492, 496. Turner states: “A therapeutic effect of the oil-in-water vehicle of this cyclosporine emulsion might be expected, as topical application of certain lipid mixtures can accelerate epidermal barrier recovery after defined barrier insults in mice.” *Id.* at 496; *see also* Ex. 1015 (“It is important to note that the [castor oil] vehicle emulsion used in this study performed well on its own, producing significant improvement from baseline in several parameters. This suggests that the nature of the formulation contributed to the therapeutic benefits observed in all treatment groups in this study.”) at 973. The art also recognized that the therapeutic effect of castor oil may be due to ricinoleic acid, a main component of castor oil, and a known anti-inflammatory agent. A. Vieira *et al.*, *Effect of ricinoleic acid in acute and subchronic experimental models of inflammation*, 9 MED. INFLAMM. 223 (2000) (“Vieira,” Ex. 1019) at 223. Vieira states, “topical application of ricinoleic acid (RA), the main component of castor oil, exerts remarkable analgesic and anti-inflammatory effects.” Ex. 1019 at 223.

57. Castor oil’s benefits for the treatment of dry eye disease/KCS were very well known in the late 1990’s and early 2000’s. It was reported that therapeutic benefits of castor oil for treating dry eye disease/KCS led in part to the

Ophthalmic Advisory Panel for the FDA's recommendation against immediate approval of Allergan's dry eye/KCS treatment, Restasis[®], in 1999. R. Murphy, *The Once and Future Treatment of Dry Eye*, REVIEW OF OPTOMETRY 1 (2000) ("Murphy," Ex. 1020) at 5. Dr. Steven Pflugfelder, testifying before the FDA panel on behalf of Allergan, was quoted as stating, "The vehicle itself is better than any artificial tear." *Id.* As the therapeutic efficacy of the castor oil, measured by objective clinical criteria, was a consistent finding in all published results of the Allergan trials, it was well established that castor oil itself had an observable effect of a therapeutic nature. *See e.g.*, Ex. 1014 at 496 (finding "a large therapeutic effect observed in the [castor oil] vehicle group" at 496; *see also*, Stevenson, Ex. 1015. An article reporting the committee recommendation against approval concluded by stating: "In the meantime, someone should consider packaging castor oil as a treatment for dry eye. Apparently it's the next best thing to cyclosporine." Ex. 1020 at 5.

58. While castor oil and CsA were independently known to provide relief to patients suffering from dry eye disease/KCS, it was known in the art that, when possible, multiple active agents should be delivered within the same emulsion, as concurrently administering separate ophthalmic emulsions had known disadvantages: "The first drug administered may be diluted significantly by the administration of the second. On this basis, combination drug products for use in ophthalmology have considerable merit." Ex. 1016 at 823. Thus, combination CsA/castor oil emulsions such as those administered in the clinical trials discussed above, as well as in Ding '607, were well established in the art prior to September

15, 2003. *E.g.*, Kunert, Ex. 1012; Turner, Ex. 1014; Stevenson, Ex. 1015; Ding '607, Ex. 1010.

59. Safe and preferred doses of castor oil were known for topical ophthalmic administration. As discussed above, Ding '607 described eye drops comprising as much as 5.00% castor oil as being “non-irritating,” while the Allergan-sponsored Stevenson trial deemed CsA/castor oil emulsions as safe for twice daily administration. Ex. 1015 at 967. Further, Goto utilized 2% castor oil eye drops and further taught that “subjects reported the castor oil . . . mixture eye drops were the most comfortable.” Ex. 1017 at 2031. Goto further taught: “By using low-concentration oil [(2% castor oil)], we succeeded in avoiding the usual complications of oil administration, such as blurred vision and a viscous sensation.” *Id.* at 2032. Thus, emulsions containing castor oil at concentrations as high as 5.00% were known to be safe and reducing the concentration to 2.00% or below was preferred for avoiding blurred vision and viscous sensation.

IX. ASSERTED REFERENCES DISCLOSE OR SUGGEST EACH OF THE CLAIMED FEATURES OF THE '162 PATENT

A. Brief Overview of the Asserted References

60. I have reviewed several references that I believe teach or suggest the pharmaceutical compositions and methods recited in claims 1-24 of the '162 patent. By virtue of their publication dates, I understand that these references, described in more detail below, may be applied in assessing the validity of the '162 patent.

Ding '979

61. U.S. Patent No. 5,474,979 to Ding *et al.*, filed May 17, 1994 (“Ding ’979,” Ex. 1006), issued on December 12, 1995. I understand that Ding ’979 can be applied in assessing the validity of the ’162 patent claims.

62. Ding ’979 is directed to pharmaceutical compositions in the form of non-irritating emulsions containing cyclosporin A (CsA) and castor oil, which can be used to treat keratoconjunctivitis sicca (KCS)/dry eye disease. Ex. 1006 at [57]; col. 5, ll. 9-12. Ding ’979 states that “cyclosporin . . . has been found as effective in treating immune mediated [*sic*: mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom . . . The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement of restoring lacrimal gland tearing.” *Id.* at col. 1, ll. 12-39. Thus, Ding ’979 teaches that CsA could be used to treat KCS/dry eye disease by acting as an immunosuppressant and by increasing tear production.

63. Ding ’979 also discusses what was known in the art about the formulation of CsA in ophthalmic preparations, noting that, while ophthalmic solutions are typically aqueous, “the solubility of cyclosporin in water is extremely low and . . . it has been considered not merely difficult but practically impossible to prepare a pharmaceutical composition comprising cyclosporin dissolved in an aqueous medium.” *Id.* at col. 1, ll. 40-44. More specifically, Ding ’979 states that “cyclosporin has demonstrated some solubility in oily preparations containing higher fatty acid glycerides . . . [but t]hese formulations frequently produce an unpleasant sensation when applied to the eye because of stimulation or the viscousness which is characteristic of these oils.” *Id.* at col. 2, ll. 40-45. Ding ’979,

however, teaches that “[i]t may be possible to minimize the problems related to unpleasant sensation and syndrome exacerbation by reducing the oil content and dispersing the oil phase into water into an emulsion.” *Id.* at col. 2, ll. 58-61.

64. Claims 7 and 8 of Ding ’979 recite emulsions having CsA and castor oil ranging from highs of 0.40% and 5.00% to lows of 0.05% and 0.625%, each respectively, while holding the other ingredients constant. *Id.* at col. 4, ll. 31-43 (Example 1). Ding ’979 states that its invention yields “an emulsion with a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues.” *Id.* at col. 2, l. 67 – col. 3, l. 3.

65. Example 1 of Ding ’979 describes five cyclosporin-containing castor oil emulsions having CsA and castor oil concentrations within the ranges recited in claims 7 and 8. *Id.* at col. 4, ll. 32-43. These five example emulsions identify four specific amounts of CsA, and combine these amounts of CsA with the four castor oil vehicles disclosed in Example 2, such that the emulsions in Example 1 all have CsA-to-castor oil ratios that fall within the more preferred range described by Ding ’979. Two additional emulsions, using the amounts of CsA and castor oil described in Examples 1 and 2, also fall within this more preferred range, and are readily envisioned based on the disclosures in Ding ’979—a 0.1% CsA/2.5% castor oil emulsion, and a 0.05% CsA/1.25% castor oil emulsion. In addition to castor oil, the emulsion vehicles disclosed in Example 2 of Ding ’979 all contain 1.00% of polysorbate 80, 0.05% Pemulen[®], an acrylate[]/C10-30 alkyl acrylate cross-polymer, 2.20% glycerine, as well as sodium hydroxide and water as needed. *Id.* at col. 4, ll. 4-5, 44-54. The percentages in Ding ’979 are all weight

percentages. *Id.* at col. 4, ll. 27-29. The disclosed emulsions have pH values in the range of 7.2 and 7.6. This pH range was well known as useful for ophthalmic emulsions. *E.g.*, Ex. 1016 at 825 (“Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4.”).

66. The example emulsion vehicles disclosed by Ding ’979 in Example 2 vary only by castor oil concentration (ranging from 0.625% to 5.00%), and are shown below:

	<u>Example 2</u>			
	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

Id. at col. 4, ll. 44-53.

67. Example 1 of Ding ’979 expressly discloses using emulsion vehicles C and D (having castor oil weight percentages of 1.25% and 0.625%) with CsA at weight percentages of 0.05% and 0.10%, as 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

Id. at col. 4, ll. 32-43.

68. As shown in the table above, Ding '979 discloses five examples of cyclosporin-containing castor oil emulsions, A-E, which contain 0.40%/5.00%, 0.20%/5.00%, 0.20%/2.50%, 0.10%/1.25%, and 0.05%/0.625% CsA/castor oil. Examples 1A, 1C, 1D, and 1E have CsA/castor oil ratios of 0.08, while Example 1B has a CsA /castor oil ratio of 0.04. Moreover, Examples 1A- 1E have castor oil/polysorbate 80 ratios of 5, 5, 2.5, 1.25, and 0.625. Each emulsion in Example 1 is consistent with the teachings of Ding '979 that the preferable weight ratio of CsA to castor oil is below 0.16, and more preferably between 0.02 and 0.12, and the more preferable weight ratio of castor oil to polysorbate 80 is between 0.5 and 12.5. *Id.* at col. 3, ll. 16-20.

69. Ding '979 mentions that these emulsions are notable, because they have “high comfort level[s] and a low irritation potential” (*id.* at col. 3, l. 1), which is unlike prior art CsA/castor oil emulsions that Ding notes were “irritating.” *Id.* at col. 3, l. 45.

70. The emulsions described in Example 1, shown above, were compiled for “treatment of keratoconjunctivitis sicca (dry eye) syndrome.” *Id.* at col. 5, ll. 11-12. In addition, studies were performed “without the active ingredient cyclosporin utilized to determine the toxicity of the emulsified components.” *Id.* at col. 5, ll. 9-14. As taught by Ding ’979, even after the emulsions, both with and without CsA, were administered to rabbit eyes eight times a day for seven days, they were found to cause “only slight to mild discomfort and slight hyperemia” with “no changes in the surface tissue” when examined by slit lamp. *Id.* at col. 5, ll. 14-19. Ding ’979 further notes that, following administration of the “cyclosporin containing castor oil emulsion,” “the therapeutic level of cyclosporin was found in the tissues of interest after dosage.” *Id.* at col. 5, ll. 21-22.

71. Thus, Ding ’979 teaches emulsions for the treatment of KCS (dry eye) which contain 0.05% CsA in castor oil, as well as emulsions which contain CsA in 1.25% castor oil. *Id.* at col. 4, ll. 32-43. Ding ’979 also teaches emulsions with a CsA/castor oil ratio of 0.04. *Id.* at Example B. Each of these emulsions also contains 1.00% polysorbate 80, 0.05% Pemulen[®] (acrylate/C10-C30 alkyl acrylate cross-polymer), 2.20% glycerine, sodium hydroxide, and water. *Id.* Ding ’979 further teaches use of these emulsions “for the treatment keratoconjunctivitis sicca (dry eye) syndrome” and that the administration of the “cyclosporin containing castor oil emulsion” resulted in a therapeutic level of CsA present in ocular tissues. *Id.* at col. 5, ll. 11-12, 19-23. Ding ’979 also notes that even when administered with high frequency (*i.e.*, eight times a day), the emulsions possessed high comfort levels and low irritation potential. *Id.* at col. 2, l. 65 - col. 3, l. 3.

72. Ding '979 names "Examples 1A-1D" when discussing "formulations with cyclosporine" and the "cyclosporin containing castor oil emulsion," for which emulsions it reports finding therapeutic levels of cyclosporin, "no difference" in toxicity as compared to the emulsions without cyclosporin, and no crystallization of cyclosporin after nine months at room temperature. *Id.* at col. 5, ll.18-30. Based on the disclosure of Ding '979, a person of ordinary skill in the art would expect that any of the CsA amounts disclosed in Example 1, in combination with any of the vehicles disclosed in Example 2, would yield a non-irritating emulsion, useful in the treatment of dry eye disease/KCS if the ratio of CsA to castor oil falls within the preferred range taught by Ding '979. As discussed above, Example 1E has a CsA/castor oil ratio (0.08) and a castor oil/polysorbate 80 ratio (0.625), each falling within the preferred ratios (0.02-0.12) and (0.5-12.5) disclosed by Ding '979, just the same as all other emulsions in Example 1. Accordingly, a person of ordinary skill would reasonably expect, based on the disclosure of Ding '979, that a composition comprising 0.05% CsA would be effective in treating dry eye disease/KCS. As noted by the applicants, it would be an error to suggest otherwise. Ex. 1005 at 0435-37.

Sall

73. K. Sall *et al.*, *Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease*, 107 OPTHALMOLOGY 631 (2000) ("Sall," Ex. 1007) was published in 2000. I understand that Sall can be applied in assessing the validity of the '162 patent claims.

74. Sall is a “multicenter, randomized, double-masked” Phase 3 clinical trial sponsored by Allergan. Ex. 1007 at 632. The trial involved the parallel assessment of the efficacy and safety of a 0.05% CsA in castor oil emulsion and a 0.10% CsA in castor oil emulsion as compared to a control vehicle (the same castor oil emulsion except that it did not contain CsA) for the treatment of dry eye disease/KCS. *Id.*; (citing studies about KCS to support assertions about the population suffering from dry eye disease). The CsA/castor oil emulsions as well as the control vehicle were administered twice a day, and parameters such as corneal staining, Schirmer tear values, blurred vision, and artificial tear use were tracked and recorded. *Id.* Sall also measured trough-level blood concentrations of CsA. *Id.* at 633, 637.

75. 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. Sall reported that treatment with either percentage of CsA provided “excellent safety” and “significantly greater improvements than vehicle” for treating dry eye disease/KCS when measured by corneal staining and Schirmer values, and that there was “no dose-response effect” between the two concentrations of CsA. *Id.* Sall also concluded that treatment with 0.05% CsA significantly reduced blurred vision and the need for artificial tears. *Id.* Sall summarized the results as follows:

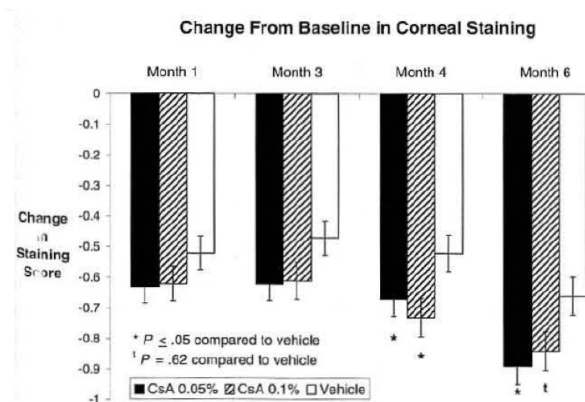
Treatment with CsA, 0.05% or 0.1% gave significantly ($P \leq 0.05$) greater improvements than vehicle in two objective signs of dry eye disease (corneal staining and categorized Schirmer values). CsA 0.05% treatment also gave significantly greater improvements ($P \leq$

0.05) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment). There was no dose-response effect. Both CsA treatments exhibited an excellent safety protocol.

Id.

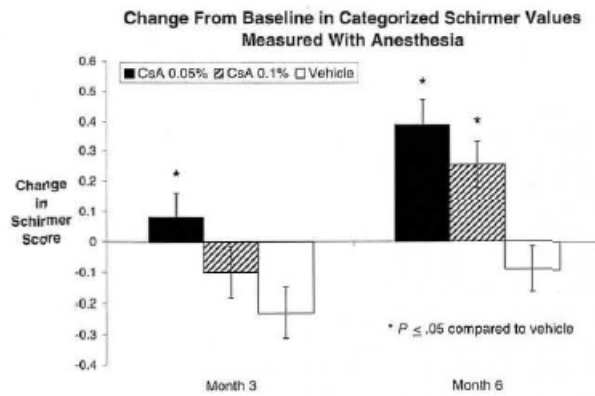
76. As discussed above, Sall monitored corneal staining as a measure of the efficacy of the 0.05% and 0.10% CsA in castor oil emulsions as compared to the vehicle control, in which a negative change from baseline indicated improvement. *Id.* at 633. After administration of the CsA emulsions and vehicle control for a period of six months, Sall noted “a statistically significant improvement from baseline in corneal staining (decrease in mean score) within all treatment groups at all follow up visits,” and a “significantly greater” improvement in corneal staining “in both CsA groups” compared to the vehicle group at month 4, “and in the CsA 0.05% group at month 6.” *Id.* at 635. In other words, Sall teaches that the 0.05% CsA emulsion of the castor oil vehicle was at least as effective at reducing corneal staining as the 0.10% emulsion of the otherwise identical castor oil emulsion vehicle. Figure 1 from Sall is reproduced below:

Figure 1
of Sall, Ex. 1007

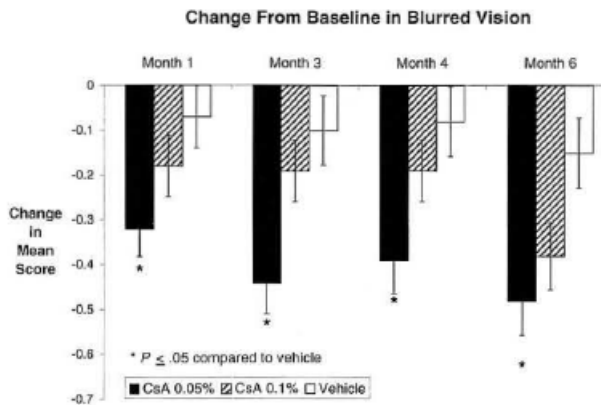


77. Sall similarly assessed efficacy of the 0.05% and 0.10% CsA/castor oil emulsions by administering Schirmer Tear Tests, in which a positive change from baseline indicated improvement. *Id.* at 633. Sall reports that, after three months of treatment, “there was a significant worsening with the vehicle group” and “a significant difference among the treatment groups, with the CsA 0.05% group significantly greater than the vehicle group.” *Id.* at 635. At three months of treatment, Figure 2 in Sall depicts negative changes in Schirmer values (indicating worsening dry eye disease/KCS) for both the CsA 0.10% treatment and the vehicle, and a positive change (indicating improvement) for the CsA 0.05% treatment. *Id.*

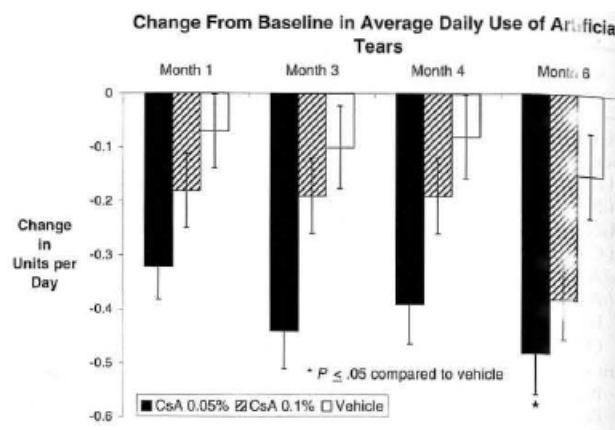
78. After six months of treatment, Sall notes that “there was a statistically significant improvement from baseline within both CsA groups” and that “changes in Schirmer values in each of the CsA groups was significantly better than the vehicle group.” *Id.* At six months of treatment, Figure 2 in Sall depicts a negative change in Schirmer value (indicating worsening dry eye disease/KCS) for the vehicle, and positive changes (indicating improvement) for both CsA treatments, with the CsA 0.05% treatment having an average change in Schirmer score more than one standard deviation higher (better) than the CsA 0.10% treatment. *Id.* Based on these results, a person of ordinary skill in the art would reasonably expect success in making a 0.05% CsA emulsion at least as effective as a 0.10% CsA emulsion for increasing tear production. Figure 2 from Sall is reproduced below:



79. Sall also assessed “symptoms of dry eye disease.” *Id.* at 636. For example, Sall assessed “subjective ocular symptoms” including blurred vision. *Id.* At all follow-up visits, statistically significant differences (less vision blurring as compared to baseline before treatment) were observed in patients receiving either CsA-containing emulsions, and the improvement in patients receiving the 0.05% CsA emulsion was “significantly greater” than in those patients receiving the castor oil control vehicle. *Id.* Thus, Sall taught that adding the 0.05% CsA to the castor oil control vehicle reduced vision blurring as compared to both the baseline (before treatment) and the vehicle alone. Figure 3 from Sall is reproduced below:



80. Sall also measured patients' use of artificial tears as a proxy for symptom relief. As assessed by Sall, "[w]ithin both CsA groups, there were statistically significant decreases in artificial tear use at months 3, 4, and 6," whereas the vehicle group showed a statistically significant decrease only at month 4. *Id.* At month 6, the decrease in artificial tear use in the CsA 0.05% group was significantly greater than in the vehicle group. *Id.* This decrease in artificial tear use may indicate a decrease in eye irritation, an adverse event associated with dry eye disease and the topical administration of ophthalmic emulsions. Figure 4 from Sall is below:



81. Sall also teaches that the concentration of CsA in the blood immediately before the next administration of the emulsion (known as the trough blood level concentration), was below the limit of quantitation (below 0.1 ng/mL) with the 0.05% CsA emulsions. In some patients receiving the 0.10% CsA emulsions, the bloodstream CsA content was quantifiable. *Id.* at 637.

82. Based on the results discussed above, Sall concludes that both the 0.05% and 0.10% CsA emulsions resulted in significant improvement in objective

signs of dry eye disease/KCS, and that the 0.05% CsA emulsion also significantly improved several subjective signs:

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 than vehicle treatment in two objective signs of dry eye disease (corneal staining and categorized Schirmer values), whereas treatment with CsA, 0.05%, resulted in significantly greater improvements than vehicle ($P \leq 0.05$) in three subjective parameters (blurred vision, use of lubricating eyedrops, and the physician's evaluation of global response to treatment). In addition, both CsA treatments were found to be exceptionally safe and well tolerated.

Id. at 638. Based on the teachings of Sall, one of ordinary skill in the art would have reasonably expected success in making the 0.05% CsA emulsion that was at least as effective at treating dry eye disease/KCS as a 0.10% CsA emulsion.

83. In assessing the efficacy of the castor oil-containing vehicle, Sall teaches that the castor oil is notably effective at relieving dry eye disease/KCS.

Sall states:

[T]he [castor oil] vehicle for the CsA ophthalmic emulsion used in this study provided substantial palliative benefits, producing significant improvements from baseline in several outcome measures. This suggests that the vehicle, and perhaps the overall formulation, contributed to the overall improvements observed in all treatment groups in this study. One of the factors contributing to the beneficial effects of the vehicle may be a sustained residence time of the oil component on the ocular surface, which may help reduce the evaporation of natural tears.

Id. at 638.

Acheampong

84. 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*, 2 LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 1001 (1998) (“Acheampong,” Ex. 1008) published in 1998. I understand that Acheampong can be applied in assessing the validity of the ’162 patent claims.

85. Acheampong evaluates CsA blood levels in humans following the twice-daily topical administration of 0.05%-0.4% CsA emulsions and the distribution of CsA in ocular tissues in animals. Ex. 1008 at 1001-02. Acheampong treated 162 human subjects with dry eye disease/KCS for a twelve-week period, testing blood CsA levels using liquid chromatography-tandem mass spectrometry (LC/MS/MS) with a lower limit of quantitation of 0.1 ng/mL. *Id.* at 1002. As noted above in paragraph 39, the specification of the ’162 patent states that “[c]yclosporin component concentrations below or less than 0.1 ng/ml are therefore considered substantially undetectable.” Ex. 1001, col. 6, ll. 1-3. Thus the lower limit of quantitation taught by Acheampong is the same limit of detection for CsA disclosed in the ’162 patent.

86. Acheampong teaches that throughout the twelve week study period, the blood concentration of CsA at both trough and peak levels was below the limit of detection for patients receiving the 0.05% CsA emulsion twice-daily. *Id.* at 1004 Table 1). Based on this data, Acheampong concluded that blood concentrations of cyclosporin were “very low” and “obviate[d] concerns about systemic toxicity.”

Ex. 1008 at 1004. Thus, Acheampong teaches that twice-daily administration of CsA emulsions which contain 0.05% CsA are safe for human use, and that even at peak levels, a 0.05% CsA emulsion does not result in detectable amounts of CsA in the blood.

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

Ex. 1008 at 1004.

Glonek

87. U.S. Patent No. 5,578,586 to Glonek *et al.*, filed February 4, 1994 (“Glonek,” Ex. 1009), issued on November 26, 1996. I understand that Glonek can be applied in assessing the validity of the ’162 patent claims.

88. Glonek is directed to emulsions for the treatment of dry eye disease, “whereby blurred vision is reduced or eliminated and the residence time of tear film on the eye is prolonged.” Ex. 1009, col. 3, ll. 5-6. Glonek describes experiments using the surfactant polysorbate 80 to stabilize oil-in-water emulsions. *Id.* at col. 19, ll. 49-51 (identifying “polysorbate sold under the trade name Tween 80” as a surfactant). An emulsion combines two immiscible phases by dispersing one in the other, such as oil dispersed in water. Ex. 1022 at 0008. An emulsifier (including a surfactant) can be used to stabilize an emulsion, retarding the natural

differentiation of the two immiscible phases into separate layers. *Id.* More stable emulsions take longer to differentiate. Consistent with this principle, Glonek teaches that higher amounts of oil require higher amounts of surfactant to stabilize the emulsion. Ex. 1009 at col. 10, l. 66 – col. 11, l. 3. In other words, increasing the oil without increasing surfactant makes the emulsion less stable, resulting in more rapid differentiation. Thus, it is an intrinsic feature of oil-in-water emulsions that increasing the oil concentration without changing surfactant concentration will result in a less stable emulsion that differentiates more rapidly.

89. Glonek teaches that that “the emulsion is preferably added to the eye as a meta-stable emulsion, not as a finely divided, stable emulsion,” (*id.* at col. 3, ll. 13-15), and that faster differentiation reduces blurring:

An emulsion is often optically opaque due to the presence of distinct dispersed phases. Therefore, an emulsion over the surface of the eye is expected to cause blurring. The duration of the blur is dependent upon the time required for the emulsion to differentiate and form separate layers replicating a tear film. Consequently, blurring is likely to occur until the emulsion differentiates.

Id. at col. 6, ll. 35-42.

Thus, in light of the teachings of Glonek, a person of ordinary skill in the art would understand that increasing the amount of oil in an emulsion, without also increasing the amount of surfactant, would necessarily result in a less stable emulsion that would break down more rapidly, thus causing less blurring.

B. Detailed Analysis of the Claims

90. As explained in detail below, it is my opinion that each and every feature of claims 1-24 of the '162 patent can be found in the prior art, including the references identified below, and one of ordinary skill in the art would have had a strong rationale for combining the references as set forth in Grounds 1-3 below, with a reasonable expectation of success, to arrive at the subject matter of each of the claims of the '162 patent.

91. Each of claims 1-24 is presented below followed by my analysis of the claims. The analysis below identifies exemplary disclosure of the cited references with respect to the corresponding claim elements, and is not meant to be exhaustive.

GROUND 1. THE TEACHINGS OF DING '979 AND SALL MAKE CLAIMS 1-10, 12-14, 16-20, AND 22-24 OBVIOUS.

92. As discussed above, Ding '979 (Ex. 1006) and Sall (Ex. 1007) can be considered prior art to the '162 patent.

Claims 1-10, 12, 18-20, and 22-24

93. Claims 1-10, 12, 18-20, and 22-24 specify various combinations of the same elements or species of the same elements. Claim 24 (which depends from claim 23) contains elements shared by the greatest number of the other claims. Thus, my analysis below groups these claims together by comparable elements using the framework of claims 23 and 24. The chart below summarizes the elements of these claims, and particular clauses and elements have been given item numbers for convenient reference:

Item	Claim 23	Claim 18	Claim 1
I.A	A method of treating dry eye disease, the method comprising the step of topically administering to an eye of a human in need thereof an emulsion . . ., the emulsion comprising:	A method of reducing side effects in a human being treated for dry eye syndrome, the method comprising the step of topically administering to the eye of the human in need thereof an emulsion . . ., wherein the emulsion comprises:	A method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion . . ., wherein the emulsion comprises
I.B	at a frequency of twice a day	at a frequency of twice a day	at a frequency of twice a day
II	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,
III	castor oil in an amount of about 1.25% by weight;	castor oil in an amount of about 1.25% by weight;	See Item IX below
IV	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80 in an amount of about 1.0% by weight;	polysorbate 80, Claim 7 (1.0%)
V	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 of about 0.05% by weight;	acrylate/C10-30 alkyl acrylate cross-polymer, Claim 8 (0.05%)
VI	glycerine in an amount of about 2.2% by weight;	a tonicity component or a demulcent component in an	Claims 2 (tonicity/ demulcent agent); 3, 6 (glycerine);

		amount of about 2.2% by weight; Claim 20 (glycerine)	and 9-10 (2.2%)
VII	sodium hydroxide; and	a buffer; and Claim 19 (sodium hydroxide)	Claims 4, 6, 9 (buffer) and 5, 10 (sodium hydroxide)
VIII	water;	water;	water,
IX	<i>See Item III</i> above	<i>See Item III</i> above	and castor oil in an amount of about 1.25% by weight; and
X	wherein the emulsion is effective in treating dry eye disease.	Claim 22 (wherein the emulsion is effective in treating dry eye disease.)	wherein the topical ophthalmic emulsion is effective in treating dry eye disease.
XI	Claim 24 (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.	Claim 12 (pH in the range of about 7.2 to about 7.6)

94. Ding '979 discloses cyclosporin A ("CsA") emulsions that are "suitable for topical application to ocular tissue." Ex. 1006, col. 6, ll. 3-7. Ding '979 notes that CsA increases tear production in the eye: "The activity of cyclosporins, as hereinabove noted, is as an immunosuppressant and in the enhancement or restoring of lacrimal gland tearing." *Id.* at col. 1, ll. 37-39. Ding '979 discloses that cyclosporin "has been found as effective in treating immune

medicated [*sic*: mediated] keratoconjunctivitis sicca (KCS or dry eye disease) in a patient suffering therefrom.” Ex. 1006, col. 1, ll. 10-16. Indeed, Ding ’979 discloses that its emulsions “were made for treatment of keratoconjunctivitis sicca (dry eye) syndrome.” *Id.* at col. 5, ll. 9-11. Thus, Ding ’979 teaches a person of ordinary skill in the art to topically administer the CsA-containing emulsions of Ding ’979 to a human eye to treat dry eye disease.

95. Ding ’979 thereby teaches “topically administering to the [an] eye of a [the] human in need thereof an emulsion,” as recited in independent claims 1, 18, and 22 (*see* **Item I.A** in my table above). Ding ’979 also thereby teaches “treating dry eye disease” with a topical ophthalmic emulsion “wherein the emulsion is effective in treating dry eye disease” in claims 1, 22, and 23 (**Item X**).

96. Moreover, the emulsions disclosed in Ding ’979 contain every ingredient of the emulsion described in claims 1-24. Ding ’979 teaches ophthalmic emulsions that contain CsA and castor oil (**Items II, III, IX**) within specified percentage ranges and in specified ratios to one another and to polysorbate 80. For example, the emulsions of claims 7 and 8 of Ding ’979 recite percentages of CsA and castor oil ranging from highs of 0.40% and 5.00% to lows of 0.05% and 0.625%, each respectively, while holding the other ingredients constant. *Id.* at col. 4, ll. 31-43 (Example 1).

97. For illustration purposes, Example 1 of Ding ’979 describes five emulsions having CsA and castor oil percentages within the ranges recited in Ding ’979 claims 7 and 8, as well as having all of the other ingredients of the emulsions recited in claims 1-24 of the ’162 patent. *Id.* at col. 4, ll. 32-43. In addition to CsA

and castor oil, the emulsions disclosed in Example 1 of Ding '979 all contain 1.00% of polysorbate 80 (**Item IV**), 0.05% Pemulen[®] (**Item V**), 2.20% glycerine (**Item VI**), as well as sodium hydroxide (**Item VII**) and water (**Item VIII**) as needed. *Id.* at col. 4, ll. 4-5, 32-43. All percentages are weight percentages. *Id.* at col. 4, ll. 27-29.

98. These ingredients (**Items II-IX, and XI**) and percentages exactly match the ingredients and percentages of the emulsion specified in claims 1-24 of the '162 patent. The 1.0% polysorbate 80 ingredient in Ding '979 is the same as the polysorbate 80 of claims 1-24 and the 1.0% polysorbate 80 of claims 7, 18 and 23 (and dependent claims) (**Item IV**). Pemulen[®] is an “acrylate[]/C10-30 alkyl acrylate cross-polymer” (Ex. 1006, col. 4, ll.4-5), and thus Ding '979 teaches the acrylate/C-10-30 alkyl acrylate cross-polymer as recited in claims 1-24 and the 0.05% weight percentage limitation for that ingredient in claims 8, 18, and 23 (**Item V**). As disclosed by claims 3 and 20 of the '162 patent and the specification (Ex. 1001, col. 11, l. 61 – col. 12, l. 3), the 2.2% glycerine satisfies the tonicity/demulcent agent/component, glycerine, and 2.2% glycerine elements of claims 2, 3, 6, 9-10, 18, 20, and 23-24 (**Item VI**). As disclosed by claims 5, 10, and 19 of the '162 patent and the specification, sodium hydroxide qualifies as the buffer and sodium hydroxide elements recited in claims 4-6, 9-10, 18-19, and 23-24 (**Item VII**). The water ingredient in Ding '979 is identical to that in claims 1-24 (**Item VIII**). Example 1 of Ding '979 also discloses that the emulsions have pH of 7.2-7.6, thereby disclosing the pH range recited in claims 12, 18, and 24 (**Item XI**). The emulsions' ingredients in Example 1 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

Id. at col. 4, ll. 32-43.

99. Ding '979 also discloses the weight percentages of CsA and castor oil claimed in claims 1-24 of the '162 patent. For illustration purposes, Example 1 specifies that the percentage of CsA may be 0.05% and that the percentage of castor oil may be 1.25%. *Id.* at col. 4, ll. 32-43. For example, 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. *Id.* at col. 3, ll. 16-20. Moreover, Example 1 itself provides an even narrower range of CsA to castor oil ratios, as each of Examples 1A-1E have ratios of 0.08 or 0.04. *See* ¶¶ 68, 71, above. An emulsion containing 0.05% CsA and 1.25% castor oil has a CsA-castor oil ratio of 0.04, which falls squarely within the preferred, more preferred, and Example 1 ratio ranges taught in Ding '979. Indeed, the 0.05% CsA / 1.25% castor oil emulsion (ratio: 0.04) is one of only two more preferred emulsions for the 1.25% castor oil vehicle (Example 2C), the other being 0.10% CsA / 1.25% castor oil as in Example 1D (ratio: 0.08). Ex. 1006 at col. 4, ll. 15-17; *id.* at col. 4, ll. 44-53. A person of ordinary skill in the art would immediately recognize Ding '979's emulsions to include an emulsion

containing 0.05% CsA and 1.25% castor oil, together with the remaining ingredients that were held constant in Example 1. The formulation of such an emulsion would be a routine matter in light of the teachings of Ding '979, as Ding '979 explicitly teaches the formulation and administration of emulsions with each of the respective ingredients. Ex. 1001, col. 14, ll. 22-24 (“These compositions are produced in accordance with well known techniques.”)

100. A person of ordinary skill had good reason to treat dry eye disease using a castor oil emulsion with 0.05% CsA and 1.25% castor oil within the preferred ratio ranges taught by Ding '979. Like Ding '979, Sall also discloses topical ophthalmic castor oil in water emulsions that contain CsA. Sall describes a “multicenter, randomized, double-masked” Phase 3 clinical trial sponsored by Allergan. Ex. 1007 at 632. The trial involved the parallel assessment of the efficacy and safety of a 0.05% CsA in castor oil emulsion and a 0.10% CsA in castor oil emulsion as compared to a control vehicle (the same castor oil emulsion except that it did not contain CsA) for the treatment of dry eye disease. *Id.* The CsA/castor oil emulsions as well as the control vehicle were administered to patients in separate groups twice a day (**Item I.B**) and parameters such as corneal staining, Schirmer tear values, blurred vision, and artificial tear use were tracked and recorded. *Id.* In describing the methods of the clinical trial, Sall notes, “patients were treated twice daily with either CsA, 0.05% or 0.1%, or vehicle” (Ex. 1007 at 631), thereby teaching administration “at a frequency of twice a day” as in claims 1, 18, and 23 (**Item I.B**).

101. Sall teaches the intrinsic property 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. 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 that there was “no dose-response effect” between the two percentages of CsA. *Id.* As noted by Allergan during prosecution, “Results . . . illustrating the change from baseline in corneal staining and change from baseline in Schirmer Score [are] key objective testing measures for dry eye [disease].” Ex. 1004 at 0208. The results of the Schirmer test in Sall confirm that the 0.05% CsA-castor oil emulsion was effective in treating patients with dry eye disease (**Item X**). *Id.* (“The mean categorized Schirmer values . . . with the CsA 0.05% group [were] significantly greater than the vehicle group.”). Based on the teachings of success in Sall, one of ordinary skill in the art would have reasonably expected success in making the castor oil emulsion vehicle of Ding ’979 containing 0.05% by weight CsA that was at least as safe and effective at treating dry eye disease as a castor oil emulsion containing 0.10% by weight CsA.

102. In addition to teaching that the 0.05% CsA emulsion would be at least as effective as the 0.10% CsA emulsion at treating dry eye, Sall also provides reasons to select the 0.05% CsA emulsion. For example, Sall reported superior results for the 0.05% CsA emulsion with regard to three subjective parameters, but reported no such results for the 0.10% CsA emulsion:

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). CsA 0.05% treatment also gave significantly greater improvements ($P < 0.05$) in three subjective measures of dry eye disease (blurred vision, need for concomitant artificial tears, and the physician's evaluation of global response to treatment).

Ex. 1007 at 631.

103. Sall further teaches that treatment with 0.05% CsA resulted in a decrease of adverse events as compared to the 0.10% CsA emulsion (**Item I.A**, claim 18). Sall states: "Overall, 25.3% (74/293) of patients treated with CsA 0.05%, 29.1% (85/292) of patients treated with CsA 0.1%, and 19.5% (57/292) of patients treated with the vehicle experienced one or more treatment-related adverse events." Ex. 1007 at 636. Sall also teaches that patients receiving the 0.05% CsA treatment experienced less occurrences of burning eye, stinging eye, conjunctival hyperemia, visual disturbances, and eye pain, as compared to the 0.10% CsA treatment group. *Id.* Although Sall does not indicate whether this trend is statistically significant, as Sall described both emulsions to be efficacious at treating dry eye disease, the decrease in adverse events and side effects provided the skilled artisan with additional reasons to formulate the emulsion with 0.05% CsA instead of 0.10% CsA.

104. Moreover, selecting a lower 0.05% CsA percentage over the 0.10% CsA percentage would generally decrease the cost of production of the emulsion

and reduce the propensity of the highly lipophilic CsA to crystallize out of solution. *See* Ex. 1006, col. 3, ll. 58-63 (crystallization).

105. Although Sall discloses an ophthalmic emulsion comprising 0.05% CsA in a castor oil emulsion vehicle, Sall does not explicitly state the percentage of castor oil in the control vehicle. Nonetheless, Sall's teaching that the 0.05% CsA emulsion is at least as effective with fewer adverse events than the 0.10% CsA emulsion provides an additional reason to use the 0.05% CsA percentage taught by Ding '979, together with 1.25% castor oil emulsion vehicle as also taught by Ding '979.

106. A person of ordinary skill in the art would reasonably understand Sall as disclosing that the same castor oil vehicle is used for both the 0.05% and 0.10% CsA emulsions. *See* Ex. 1007 at Figs. 1-4 (each showing a single vehicle control group for comparison to both the 0.05% and 0.10% CsA emulsion groups), 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"). Because Sall refers to only one vehicle control for comparison to both the 0.05% and the 0.10% CsA emulsions, a person of ordinary skill in the art would reasonably understand Sall as teaching that both emulsions were otherwise identical, including the percentage of castor oil.

107. Thus, Sall discloses 0.10% and 0.05% CsA emulsions in a common vehicle. Ex. 1006 at 632. As discussed previously, Ding '979 teaches more preferred ratios of CsA-to-castor oil between 0.12 to 0.02 (*id.* at col. 3, ll. 17-20), and each of Ding's working examples of CsA emulsions have CsA-to-castor oil

ratios of 0.08 or 0.04. Only one castor oil vehicle taught by Ding '979, the 1.25% castor oil of Example 2C, would have yielded an emulsion having a more preferred ratio of CsA-to-castor oil for the CsA amounts used in Sall, 0.05% and 0.10%. *See* Ex. 1006, col. 4, ll. 32-54. Specifically, a 0.10% CsA / 1.25% castor oil emulsion would have had a ratio of 0.08, and a 0.05% CsA / 1.25% castor oil emulsion would have had a ratio of 0.04. Sall provides good reasons to formulate 0.05% CsA in castor oil to treat dry eye disease/KCS, and the 1.25% castor oil is the only vehicle of Ding '979 for which both the 0.05% and 0.10% CsA emulsions of Sall would have a ratio in Ding '979's more preferred range. Thus, a person of ordinary skill would have had a well-founded rationale to formulate 0.05% CsA in 1.25% castor oil based on the combined teachings of the references.

108. My conclusion that a person of ordinary skill would immediately recognize a 0.05% CsA / 1.25% castor oil emulsion as taught by Ding '979 is consistent with the statements by the applicants during the prosecution of the parent '857 application that a person of ordinary skill in the art "would readily envisage" the emulsion of Ding '979 comprising both 0.05% CsA and 1.25% castor oil and would make it with a reasonable expectation of success:

One need only use the cyclosporin concentration of Example 1E (0.05%), the castor oil concentration of Example 1D (1.250%), and the remaining ingredients of those examples. . . [O]ne of ordinary skill in the art 'would readily envisage' such a composition, especially in view of [Ding '979] 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% ($0.05\% / 0.04 = 1.25\%$). 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 . . . are too small to believe otherwise. The formulation of Composition II is squarely within the teaching of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise[.]

Ex. 1005 at 0435.

109. Thus, as recited in claims 1, 18, and 23 a person of ordinary skill in the art would have had good reason to administer twice a day (**Item I.B** in my table following paragraph 93, above) an emulsion topically to the eye of a human being in need thereof (**Item I.A**), the emulsion comprising CsA in an amount of 0.05% by weight (**Item II**), castor oil in an amount of 1.25% by weight (**Items III and IX**), polysorbate 80 (**Item IV**), acrylate/C10-30 alkyl acrylate cross-polymer (**Item V**), glycerine (a tonicity agent/component or demulcent component) (**Item VI**), sodium hydroxide (a buffer) (**Item VII**), and water (**Item VIII**). Moreover, the skilled artisan would have reason for the polysorbate 80 to be 1.0% by weight, the acrylate/C10-30 alkyl acrylate cross-polymer to be 0.05% by weight, the glycerine to be about 2.2% by weight, and the pH of the emulsion to be in the range of 7.2-7.6 (**Item XI**). In light of the teachings of Ding '979 and Sall, a person of ordinary skill in the art would have had good reason to expect that this emulsion would be effective in treating dry eye disease (**Item X**) as well as result in reduced side effects (**Item 1.A**, claim 18). In other words, the respective combinations of elements in each of claims 1-10, 12, 18-20, and 22-24 would have been obvious to a person of ordinary skill, as disclosed by Ding '979 and Sall.

Claim 13:

“The method of claim 1, wherein the emulsion is as substantially therapeutically effective as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.”

Claim 14:

“The method of claim 1, wherein the emulsion achieves at least as much therapeutic effectiveness as a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.”

110. As discussed above with respect to claim 1, a person of ordinary skill would have had good reason to combine Sall’s teaching of twice-daily ophthalmic administration of the 0.05% CsA in castor oil emulsion to increase tear production to Ding ’979’s disclosure of the 1.25% castor oil vehicle (Example 2C) for delivering 0.05% CsA to increase tear production.

111. Claims 13 and 14 are comparative in nature, comparing the therapeutic efficacy of 1.25% castor oil emulsions containing 0.05% CsA or 0.10% CsA. As discussed previously in the context of claim 1, a person of ordinary skill in the art would have considered the ophthalmic emulsions disclosed in Ding ’979 in view of Sall’s teachings that there was “no dose-response effect” between the castor oil emulsions containing 0.05% CsA or 0.10% CsA and that the 0.05% CsA

emulsion was at least as therapeutically effective as the 0.10% CsA emulsion. One would thereby have arrived at the methods of claims 13 and 14.

112. In discussing the outcomes of the clinical trial assessing the safety and efficacy of twice-daily administrations of castor oil in water emulsions containing 0.05% CsA and 0.10% CsA, Sall teaches: “[T]he most important overall finding was that topical treatment with either CsA 0.05% or 0.1% resulted in significantly greater improvements than vehicle treatment in two objective signs of dry eye disease (corneal staining and categorized Schirmer values).” Ex. 1007 at 637. Sall further emphasizes that there was “no dose-response effect” between the two emulsions, and notes several measurements in which both the 0.05% emulsion and the 0.10% emulsion resulted in statistically significant improvements from the baseline. Ex. 1007 at 631, 634-36. For example, Sall teaches: “At month 6, there was a statistically significant improvement [in the Schirmer Tear Test] from baseline within both CsA groups.” *Id.* at 635. Out of the many objective and subjective parameters utilized to assess the therapeutic nature of the CsA emulsions, no results indicated that the 0.10% emulsion was statistically significantly better than the 0.05% emulsion. Thus, based on these teachings, a person of ordinary skill in the art would have expected that a 0.05% CsA/1.25% castor oil emulsion would have been “as substantially therapeutically effective as” an emulsion comprising 0.10% CsA/1.25% castor oil, as recited in claim 13.

113. A similar analysis applies for the method of claim 14, wherein a 0.05% CsA/1.25% castor oil emulsion “achieves at least as much therapeutic effectiveness as a second emulsion” which comprises 0.10% CsA/1.25% castor oil.

Sall teaches that the 0.05% CsA and castor oil emulsion was at least as therapeutically effective as the 0.10% CsA and castor oil emulsion. A person of ordinary skill in the art would have a reasonable expectation of success in making a 0.05% CsA in castor oil emulsion that was at least as therapeutically effective as a castor oil emulsion containing 0.10% CsA as studies had previously shown that topical ophthalmic administration of 0.05% CsA was at least as effective as 0.10% CsA in reducing immunogenic markers associated with the immune-mediated response that sometimes contributes to dry eye disease/KCS. Ex. 1014 (Turner) at 496 (“The most important finding of the present study was that normalized IL-6 levels significantly decreased from baseline after 6 months of treatment with 0.05% CsA, whereas the decreases seen after treatment with either 0.1% CsA or vehicle were not statistically significant.”). Accordingly, based on the teachings of Sall, a person of ordinary skill in the art would have had good reason to expect that a 0.05% CsA/1.25% castor oil emulsion would have achieved “at least as much therapeutic effectiveness as” an emulsion comprising 0.10% CsA/1.25% castor oil, as in claim 14.

Claim 16:

“The method of claim 1, wherein the emulsion, when administered to the eye of a human, demonstrates a reduction in adverse events in the human, relative to a second emulsion administered to a human in need thereof at a frequency of twice a day, the second emulsion comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight.”

Claim 17:

“The method of claim 16, wherein the adverse events are side effects.”

114. As discussed above with respect to claim 1, a person of ordinary skill would have had good reason to combine Sall’s teaching of twice-daily ophthalmic administration of the 0.05% CsA in castor oil emulsion to increase tear production to Ding ’979’s disclosure of the 1.25% castor oil vehicle (Example 2C) for delivering 0.05% CsA to increase tear production. Moreover, Sall discloses that the 0.05% CsA emulsion demonstrated a reduction in adverse events and undesirable side effects relative to the 0.10% CsA emulsion.

115. As discussed above in the context of claim 1, Sall demonstrated that administration of the emulsion comprising 0.05% CsA resulted in fewer adverse events than the 0.10% CsA emulsion. Specifically, Sall states: “Overall, 25.3% (74/293) of patients treated with CsA 0.05%, 29.1% (85/292) of patients treated with CsA 0.1%, and 19.5% (57/292) of patients treated with the vehicle experienced one or more treatment-related adverse events.” Ex. 1007 at 636. Thus, it was known in the art that a 0.05% CsA emulsion, when topically administered to the eye twice a day demonstrated a reduction in adverse events relative to a 0.10% CsA emulsion.

116. Sall also teaches that the 0.05% CsA emulsion resulted in fewer side effects. Although Sall does not indicate whether this trend is statistically significant, Sall teaches that patients receiving the 0.05% CsA emulsion reported less burning, stinging, and general eye pain than patients receiving the 0.10% CsA emulsion. Ex. 1007 at 636. Moreover, Sall taught that the 0.05% CsA emulsion

resulted in undetectable CsA blood levels. Thus, it was known in the art that a 0.05% CsA emulsion, when topically administered to the eye twice a day, demonstrated a reduction in side effects relative to a 0.10% CsA emulsion.

GROUND 2. THE TEACHINGS OF DING '979, SALL, AND ACHEAMPONG MAKE CLAIMS 11 AND 21 OBVIOUS.

117. As discussed above, Ding '979 (Ex. 1006), Sall (Ex. 1007), and Acheampong (Ex. 1008) can be considered in assessing the validity of the claims of the '162 patent.

Claim 11:

“The method of claim 1, wherein, when the emulsion is administered to an eye of a human, the blood of the human has substantially no detectable concentration of cyclosporin A.”

Claim 21:

“The method of claim 18, wherein, when the emulsion is administered to the eye of a human for treating dry eye syndrome, the blood of the human has substantially no detectable concentration of cyclosporin A.”

118. As discussed above with respect to claim 1, a person of ordinary skill would have had good reason to combine Sall's teaching of twice-daily ophthalmic administration of the 0.05% CsA in castor oil emulsion to increase tear production to Ding '979's disclosure of the 1.25% castor oil vehicle (Example 2C) for delivering 0.05% CsA to increase tear production.

119. Moreover, Sall teaches that there is no detectable concentration of CsA in the blood of patients receiving 0.05% CsA emulsions twice a day: “Trough

blood concentrations of CsA were below the limit of quantitation (of 0.1 ng/mL) in all samples from the CsA 0.05% group.” Ex. 1007 at 637. As noted above, the specification of the ’162 patent defines concentrations of CsA below 0.1 ng/mL as “substantially undetectable.” *See*, ¶ 39 above, citing Ex. 1001, col. 5, l. 64 – col. 6, l. 3. Thus, based on the teachings of Sall, it was known in the art prior to September 15, 2003 that the twice-daily topical ophthalmic administration of 0.05% CsA emulsions resulted in “substantially no detectable concentration of cyclosporin A” as recited in claims 11 and 21.

120. In a similar study, Acheampong measured blood CsA levels at both peak and trough levels:

[H]uman subjects with KCS receiv[ing] an eyedrop of vehicle or 0.05%, 0.1%, 0.2%, or 0.4% cyclosporine emulsion twice daily for 12 weeks. Blood samples were collected from all subjects at morning troughs after 1, 4, and 12 weeks of dosing. In addition, blood samples were collected from selected subjects at 1, 2, and 4 h after the last dose at week 12. Cyclosporin A (CsA) concentrations in blood samples were measured by a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method . . . The lower limit of quantitation of the blood assay was 0.1 ng/ml.

Ex. 1008 at 1002. Acheampong reported that patients receiving 0.05% CsA emulsions had CsA blood levels below the limit of quantitation at both peak and trough levels, as illustrated by the table, below:

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

Ex. 1008 at 1004.

121. A person of ordinary skill in the art would have had good reason to combine the teachings of Acheampong with those of Ding '979 and Sall, as Acheampong provides additional detailed teachings regarding topically administering CsA emulsions to the eye, and particularly that the blood has substantially no detectable concentration of CsA after ophthalmic treatment with 0.05% CsA in castor oil. The skilled artisan would have had a reasonable expectation of success in performing the methods recited in claims 11 and 21, based on the success reported by Sall and Ding '979 and the blood levels of CsA reported by Sall and Acheampong. In view of the foregoing, the subject matter of claims 11 and 21 would have been obvious.

GROUND 3. THE TEACHINGS OF DING '979, SALL, AND GLONEK MAKE CLAIM 15 OBVIOUS.

122. As discussed above, Ding '979 (Ex. 1006), Sall (Ex. 1007), and Glonek (Ex. 1009) can be considered in assessing the validity of the claims of the '162 patent.

Claim 15:

“The method of claim 1, wherein the emulsion breaks down more quickly in the eye of a human, once administered to the eye of the human, thereby reducing vision distortion in the eye of the human as compared to a second emulsion that contains only 50% as much castor oil.”

123. As discussed above with respect to claim 1, a person of ordinary skill would have had good reason to combine Sall’s teaching of twice-daily ophthalmic administration of the 0.05% CsA in castor oil emulsion to increase tear production to Ding ’979’s disclosure of the 1.25% castor oil vehicle (Example 2C) for delivering 0.05% CsA to increase tear production.

124. Claim 15 depends from claim 1, and adds that the emulsion breaks down more quickly in the eye than a second emulsion with only 50% as much castor oil, thereby reducing vision distortion in the eye as compared to the second emulsion. The specification notes that “a relatively high concentration of hydrophobic component is believed to provide for a more quick or rapid breaking down or resolving of the emulsion in the eye, which reduces vision distortion which may be caused by the presence of the emulsion in the eye and/or facilitates the therapeutic effectiveness of the composition.” Ex. 1001, col. 2, 43-49. The specification further provides that the breaking down of the emulsion can be “measured by split-lamp techniques to monitor the composition in the eye for phase separation.” Ex. 1001, col. 15, ll. 3-4.

125. Glonek teaches that emulsions on the ocular surface are expected to cause blurring, and that “the duration of the blurring is dependent upon the time required for the emulsion to differentiate and form separate layers.” Ex. 1009, col.

6, ll. 37-40. A person of ordinary skill would have good reason to assess the formulations of Ding '979 in view of Glonek, as Glonek teaches the positive effect of increasing the oil percentage in an oil-in-water emulsion, used in the treatment of dry eye disease. Glonek discloses oil-in-water emulsions “whereby blurred vision is reduced or eliminated” for the treatment of dry eye disease, and notes that it is preferred that the emulsion “rapidly differentiate in the eye.” *Id.* at col. 3, ll. 3-7; *id.* at col. 6, ll. 49-50. Glonek teaches that an “emulsion is preferably added to the eye as a meta-stable emulsion, not as a finely divided, stable emulsion.” (*id.* at col. 3, ll. 13-15), and that the instabilities inherent in oil-in-water emulsions are stabilized by adding surfactants. *Id.* at col. 10, l. 66 – col. 11, l. 11. Because Glonek teaches that increased amounts of oil require corresponding increases in surfactant to stabilize them, it would be apparent to a skilled artisan that doubling the oil in an emulsion while holding surfactant constant would result in a less stable emulsion, thereby reducing the visual blurring associated with excessively stable emulsions.

126. A person of ordinary skill would understand Glonek’s teaching that “the emulsion should differentiate rapidly” when “oil is added in the form of an emulsion” to confirm that the surfactant “enables rapid formation of a film” by “permit[ing an] increase in the oil content of an emulsion.” This conclusion is further confirmed by the teaching that “Larger concentrations of oil . . . provide even greater improvement [in the tear film].” *Id.* at col. 14, ll. 58 – 59. Glonek further discloses a method by which the optimal amount of oil may be determined

through adjusting the amount of surfactant present in the emulsion to reduce visual blurring. *Id.* at col. 12, l. 33 – col. 20, l. 30.

127. Moreover, Glonek also discloses that one would not want to increase the castor oil concentration too much, teaching that “if the oil component of the tear film is excessively thick or irregular (beaded), the patient will experience prolonged blurred vision.” Ex. 1009, col. 5, ll. 16-22. It was known in the art prior to September 15, 2003 that ophthalmic emulsions containing as much as 2% castor oil were not so thick as to result in visual blurring (*see*, ¶ 59, above, discussing Goto, Ex. 1017 at 2032). Thus, Glonek teaches both the “breaks down more quickly in the eye of a human” element of dependent claim 15, as well as providing additional motivation for selecting the 1.25% castor oil emulsion vehicle of Example 2C for topical ophthalmic delivery of 0.05% CsA.

X. NO UNEXPECTED RESULTS

128. In addition to my opinions regarding the obviousness of the methods claimed in the '162 patent, which are presented above, I have also considered the Schiffman and Attar declarations submitted by Allergan during prosecution claiming unexpected results. As discussed below, it is my opinion that there is no evidence of unexpected results, nor does the emulsion possess surprising, therapeutic efficacy against dry eye disease. I focus my discussion on two declarations that were identified by the examiner during prosecution as “demonstrat[ing] surprising and unexpected results.”

129. At the time he submitted his declaration, Dr. Schiffman had been an Allergan employee for 12 years and was a clinical investigator in the Phase III

clinical trial for Restasis[®]. Ex. 1004 at 0207. At that time, Dr. Attar was a Research Investigator at Allergan. *Id.* at 0233. As Dr. Attar's declaration reviews the same data as Schiffman Declaration 1, I have assessed their statements concurrently. As Dr. Schiffman's exhibits include each and every exhibit discussed by Dr. Attar, I discuss the exhibits only once using designations from Schiffman Declaration 1.

130. Both declarations acknowledge that it was previously known to treat dry eye/KCS and increase tear production by administering CsA to the eye:

It 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 to inhibit T cell activation which would lead to an increase in tear production and potentially other therapeutic effects related [to] cyclosporine's anti-inflammatory and anti-apoptotic effects and thus limit chronic inflammation in the pathology of dry eye.

Id. at 0209, *see also* 0233-34.

131. Both declarations assert that unexpected benefits were discovered using the claimed compositions and/or claimed methods. *Id.* at 0207, *see also, id.* at 0233. It is my opinion, however, that this assertion is unsupported by the data that were presented in these declarations.

132. According to Schiffman Declaration 1, "Allergan's multicenter, randomized, double-masked Phase 3 trials, . . . compared the efficacy and safety of the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil to a the [*sic*] claimed formulation (containing 0.05% by weight

cyclosporin A and 1.25% by weight castor oil), and to a vehicle containing 1.25% by weight castor oil.” Ex. 1004 at 0208. Dr. Attar makes similar references to a Phase 3 clinical trial. *Id.* at 0234-35. Drs. Schiffman and Attar appear to be referring to the Phase 3 clinical trials performed by Allergan and described in Sall (Ex. 1007).

133. As discussed in more detail above, Sall presents the results of the Allergan-sponsored Phase 3 “multicenter, randomized double-masked” clinical trials in which Allergan compared the efficacy and safety of emulsions containing 0.05% and 0.10% CsA in a castor oil emulsion vehicle. Consistent with standard scientific practices, Sall presents this data in an interpretable fashion by providing error bars that are lacking from the versions presented in the Schiffman and Attar declarations.

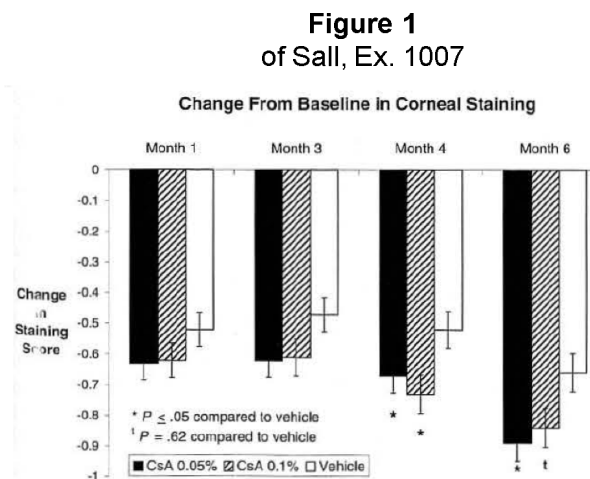
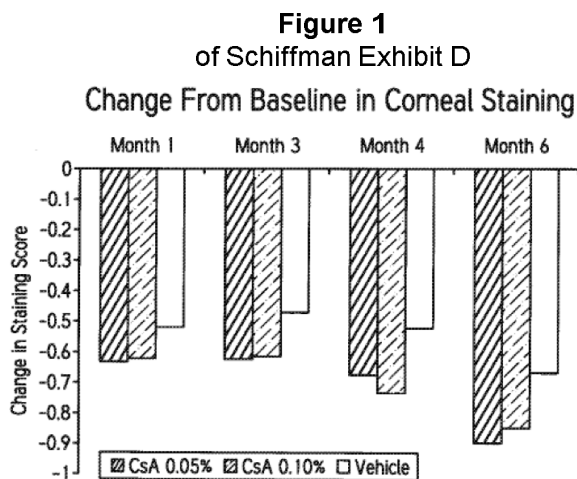
134. The first of four figures presented in Exhibit D, said by Dr. Schiffman to represent data acquired in a “multicenter, randomized, double-masked Phase 3 trial” (*id.* at 0208) conducted by Allergan, is reproduced below in ¶ 135. The adjacent Figure is from the Allergan-sponsored, “multicenter, randomized, double-masked” Phase 3 clinical trials as published by Sall. Ex. 1007. Dr. Schiffman introduces the data presented in Exhibit D as follows:

Surprisingly, the claimed formulation and method 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 according to at least four testing parameters. This result was surprising and

completely unexpected. These results are attached to this declaration in Exhibit D.

Id. at 0210 (formatting in original).

135. According to Dr. Schiffman, the first figure of Exhibit D, shown below on the left, displays the change from baseline (before treatment) in corneal staining over a six month period when comparing the instant invention's emulsion, which comprises 0.05% CsA and 1.25% castor oil, with that of Example 1D of Ding, which comprises 0.10% CsA and 1.25% castor oil. On the right is a substantively identical graph from the prior art Sall study (except that Sall included, per scientific standard practice, error bars), which compares emulsions of 0.05% CsA and 0.10% CsA to the same castor oil-based vehicle and to each other.



Id. at 0226; *see also*, Ex. 1007 at 635.

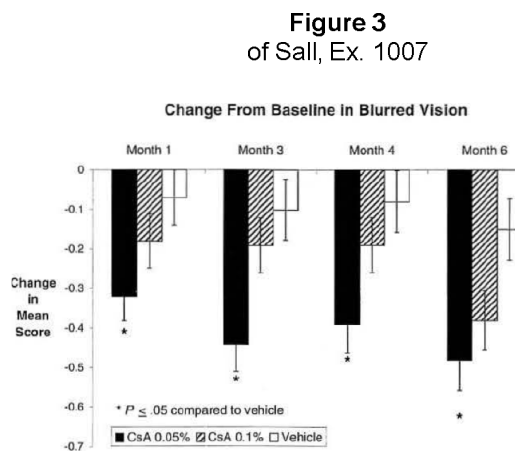
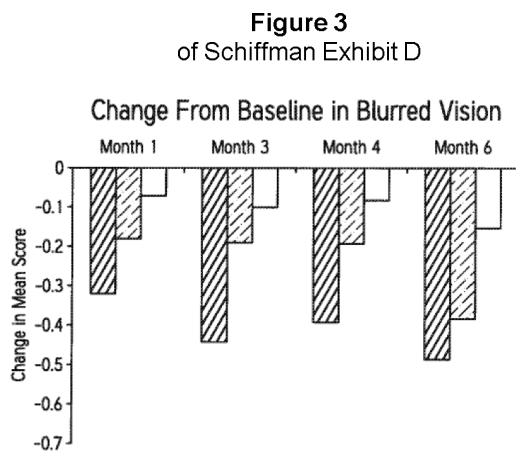
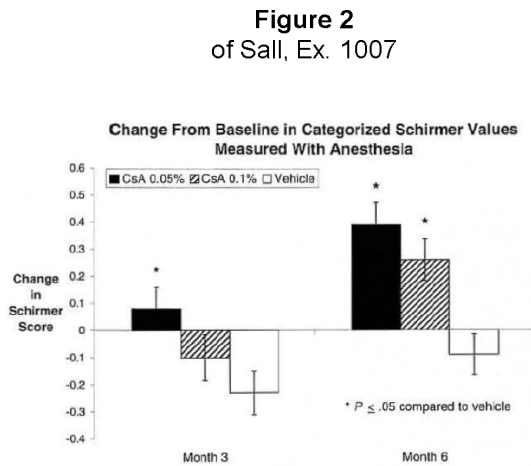
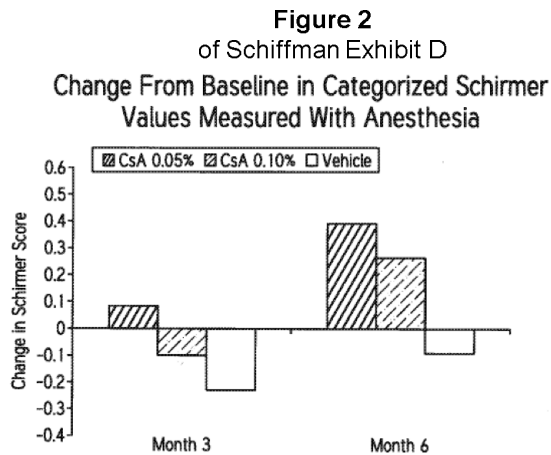
136. The figures presented in Exhibit D are characterized by Dr. Schiffman as evidence of “surprising” results. However, for data to be interpretable for the identification of unexpected results, a statistical interpretation must be possible. For a clinical trial, the number of patients involved and the raw data, or at

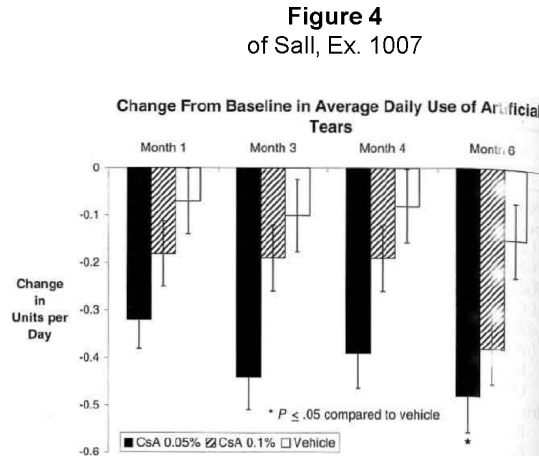
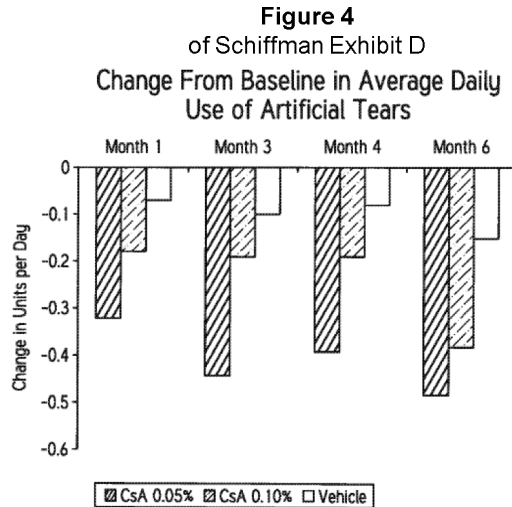
least the error rate associated with the reported numbers, are all necessary details, from which the raw data may be analyzed to form a conclusion. Without these parameters, results are difficult to interpret, and it is impossible to reach a scientifically meaningful conclusion. Moreover, data supporting a conclusion of no significant difference between the two emulsions, including error bars, were disclosed in Sall more than one year before the earliest claimed priority date of the patent, as discussed in more detail above (*see* ¶¶ 100-106) with respect to claims 1, 18, and 23 in Ground 1.

137. I compared the Schiffman/Attar declaration data to that of Sall in paragraph 135 because I believe that Sall illustrates the standard practice of including statistical measures for assessing whether the results are significant. While no such conclusion can be based on the data in the Schiffman and Attar declarations because of the absence of relevant information, Sall does include such information and can therefore answer the question of whether the results reported therein are significant. In the case of the effect of changing CsA concentration from 0.10% to 0.05%, Sall teaches that the 0.05% CsA emulsion is safe and at least as effective as the 0.10% CsA emulsion. *See* ¶¶ 100-02, above. This conclusion is consistent with the overlap in error bars observed between the two groups at each measurement, as well as by the way that neither CsA group is consistently larger than the other over time.

138. As the lack of statistical analysis discussed above also applies to Figures 2-4 of Dr. Schiffman's Exhibit D (Ex. 1004 at 0226-27), I similarly conclude that no evidence of surprising results can be derived from them. As with

Figure 1 in Exhibit D, Figures 2-4 can be compared to Figures 2-4 of Sall, for which, again, Sall derives a conclusion of “no dose-response effect.” Ex. 1007 at 631, *see* 635, for Figures 1 and 2, *see* 636 for Figures 3 and 4, *see* 635-36 for Sall’s discussion of the data presented in Figures 1-4.





139. Exhibits E and F of the Schiffman declaration (shown below) respectively provide a chart and a graph showing the ratio of “improvement in STT [Schirmer score]” and “decrease in Corneal Staining” of an the 0.05% CsA-0.625% castor oil emulsion and the 0.05% CsA-1.25% castor oil emulsion as compared to the 0.10% CsA in 1.25% castor oil emulsion. Exhibits E and F purport to show that there is no difference between the 0.05% CsA emulsion in 1.25% castor oil and the 0.10% CsA emulsion in 1.25% castor oil, but that there is a surprising and critical difference between the 0.05% CsA emulsion in 0.625% castor oil and the 0.05% CsA emulsion in 1.25% castor oil. Again, no statistical analysis is provided for this data, and thus no conclusion of surprising results can be derived.

140. Moreover, as no raw results are provided, it cannot be said that even statistically significant results would be clinically meaningful. Indeed, the scale adopted, and the variation in results using that scale, both indicate a high rate of error/natural variation. For example, each value in the table is reported as either

an integer (1 or 2) or a simple fraction ($0.25 = \frac{1}{4}$). This suggests that the table was prepared using a significant amount of rounding, providing another reason to question whether any of the reported differences are significant.

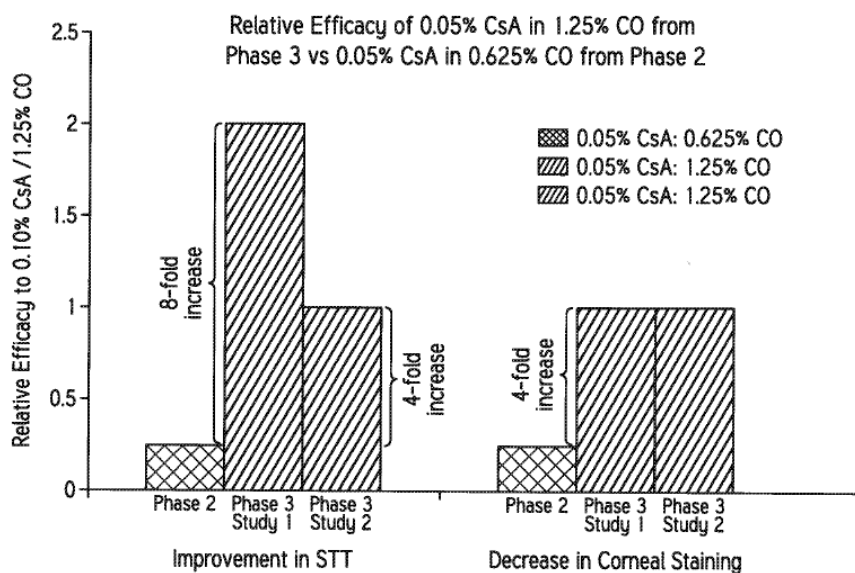
141. Moreover, the degree of variation in the results of the Schirmer Tear Test, as presented in Exhibit E, from consecutive and identical Phase 3 studies comparing 0.05% CsA/1.25% castor oil to 0.10% CsA/1.25% castor oil further suggests a high degree of error in the results. For example, as shown in Exhibit E, repetition of the same Phase 3 study reported Schirmer Tear Test comparative values of 1 and 2—a 100% difference. This indicates that the error bars for these values would be quite large, because the results for the same test changed by 100%. Thus, only differences much larger than a comparative value of 1 would be considered significant. In other words, the difference between the reported comparative value of 0.25 (for the Phase 2 study) and the reported comparative value of 1 (from the Phase 3 study) does not appear to be significantly different. Moreover, one should not compare the reported comparative value 0.25 from the Phase 2 study with the reported comparative value 2 from the first Phase 3 study because the reported comparative value 2 in the first Phase 3 study turned out to be non-repeatable.

Schiffman Declaration Exhibit E

	Phase 2 001	Phase 3 (1 st study)	Phase 3 (2 nd 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



Id. at 0229, 0231.

142. Moreover, the relevant emulsion of the '162 patent performed *exactly the same* as the prior art emulsion Example 1D of Ding '979 in three of the

four assessments presented in Exhibit D. The alleged two-fold improvement over the 0.10% CsA/1.25% castor oil emulsion did not prove to be reproducible.

143. Even if Exhibits E and F did demonstrate statistical significance and clinically meaningful results (they do not), they do not demonstrate surprising results because they merely confirm the teachings of the prior art. For example, Sall reported statistically significant improvement in Schirmer score and reductions in corneal staining for the castor oil emulsion. *See* ¶¶ 76-78 above; Ex. 1007 at 635 (noting “a statistically significant improvement from baseline in corneal staining (decrease in mean score) within all treatment groups at all follow up visits,”); *id.* at 638 (“[T]he [castor oil] vehicle for the CsA ophthalmic emulsion used in this study provided substantial palliative benefits, producing significant improvements from baseline in several outcome measures. This suggests that the vehicle, and perhaps the overall formulation, contributed to the overall improvements observed in all treatment groups in this study.”).

144. These results were consistent with other teachings in the art that the castor oil vehicle itself contributed significantly to the efficacy of the ophthalmic emulsions. *See, e.g.,* ¶¶ 54-57 above. The castor oil vehicle was known to correlate with a “large therapeutic effect.” *See e.g.,* Ex. 1014 at 496; *see also,* Stevenson, Ex. 1015. Indeed, it was reported that the therapeutic benefits of castor oil for treating dry eye disease/KCS led in part to the Ophthalmic Advisory Panel for the FDA recommending against immediate approval of Allergan’s dry eye treatment. Ex. 1020 at 5 (“The vehicle itself is better than any artificial tear.”).

145. Like Dr. Schiffman's other exhibits, Exhibit B similarly failed to provide any indication of statistical significance. Dr. Schiffman presents Exhibit B, and discusses it in relation to a "randomized, multicenter, double-masked, parallel group, dose-response controlled Phase 2 trial on several cyclosporin-A and castor oil-containing formulations." *Id.* at 0207. He states: "To the best of my knowledge, the specific cyclosporin-A containing formulations tested in humans in this Phase 2 study are disclosed in the Ding ['979] reference." *Id.* at 0208. Exhibit B is reproduced below:

Schiffman Declaration Exhibit B

Phase 2 Results - Phase 3 Target Subpopulation

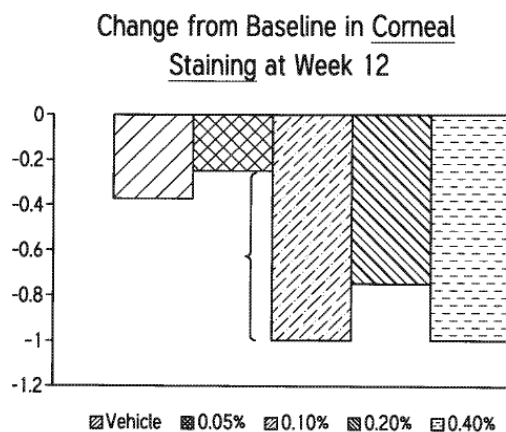


FIG. 1

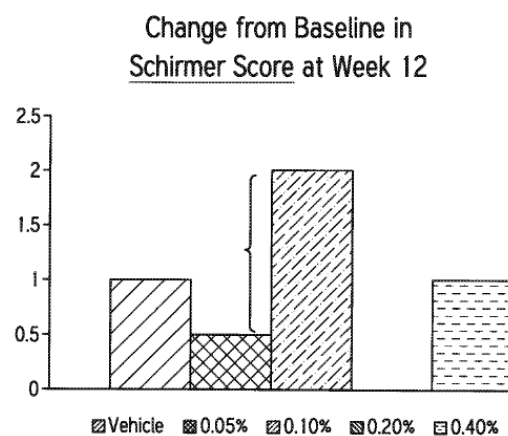


FIG. 2

Id. at 0222.

146. Based upon Dr. Schiffman's representation that the 0.10% CsA and 0.05% CsA emulsions are respectively Examples 1D and 1E from Ding '979, it must be understood that two variables were changed between each emulsion

studied: the cyclosporin A content and the castor oil content. However, with multiple changing variables it is impossible to determine which variable is responsible for any change in emulsion performance. Furthermore, it is impossible to determine whether the observed differences are statistically significant because no measure of error is available. Without the raw data and sample size, or an indication of error, it is impossible to know whether any perceived decrease in corneal staining or increase in Schirmer score actually occurred, as opposed to being attributable to chance variation.

147. Because of the absence of basic information necessary for evaluating the data in Exhibit B, 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," (*id.* at 0208, formatting in original) lacks critical support as a scientific finding. It is my opinion that a properly supported scientific conclusion that the 0.10% emulsion exhibited significant improvement over other emulsions or vehicle that were also investigated cannot be reached based on Exhibit B.

148. Indeed, my interpretation is supported by the Stevenson publication which reported the Phase 2 results of the CsA clinical trial for dry eye disease. Ex. 1015 at 967 (publication from 2000 by "The Cyclosporin A Phase 2 Study Group" reporting results of "a dose-ranging, randomized trial" of CsA). Stevenson reported the conclusions from the Phase 2 trial:

Cyclosporin A ophthalmic emulsions, 0.05%, 0.1%, 0.2%, and 0.4%, were safe and well-tolerated, 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. 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.

Id. at 967.

149. Similarly, the Stevenson Phase 2 trial found no statistically significant among-group differences at week 12 or at any other time in superficial punctate keratitis, as measured by corneal staining. *Id.* at 968, 971. Although there appear to be some minor differences between the graphs, Stevenson's Figure 2 demonstrates that a graph very similar in magnitude and trend to Exhibit B, Figure 1, does not illustrate any statistically significant result, and therefore could be the result of chance variation. *Id.* at 971. Dr. Schiffman's provision of graphs without error bars makes it impossible to establish statistically significant differences between the corneal staining results of Exhibit B, Figure 1.

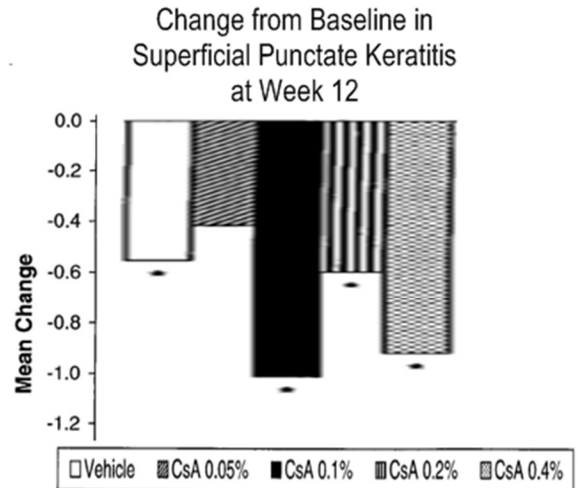
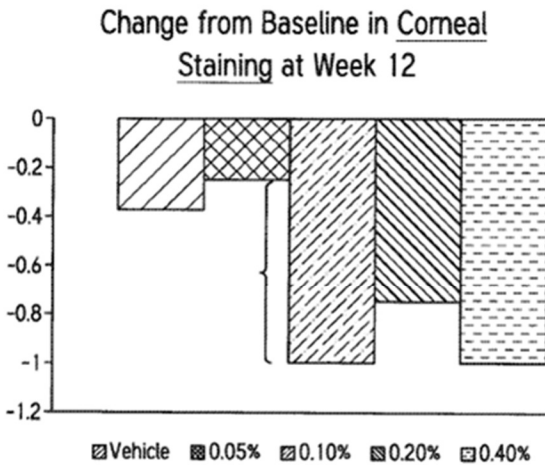


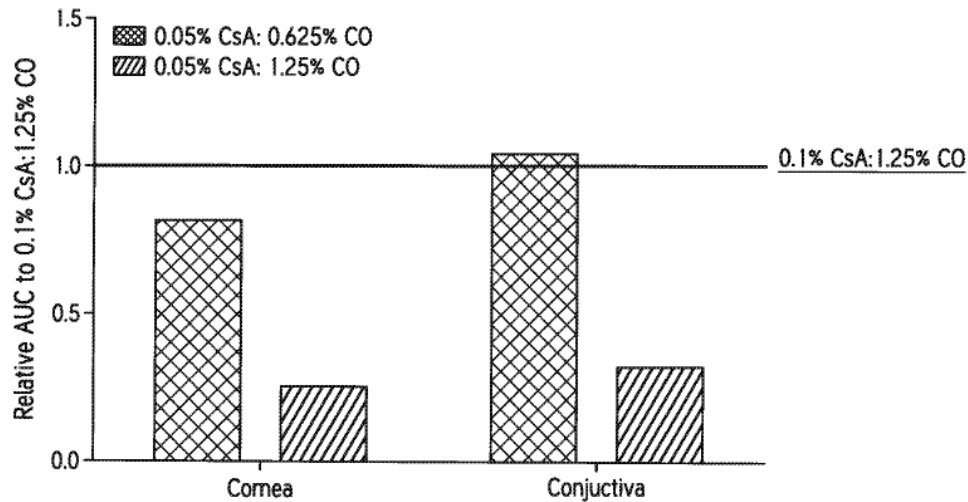
FIG. 1

Week 12 data, extracted from,
Figure 2 of Stevenson; Ex. 1015

150. With respect to the Schirmer tear tests, Stevenson reported that “[t]he only statistically significant improvement from baseline occurred in the cyclosporin A 0.4% group at treatment week 4,” and even the “most consistent improvements” with respect to *baseline* in the 0.10% CsA group “only approached statistical significance.” *Id.* at 971. In other words, Stevenson confirms that the change in Schirmer score of 2 for the 0.10% CsA group in Fig. 2 of Schiffman Exhibit B is not even statistically significantly different from 0 (baseline). The bracket drawn between the 0.05% and 0.10% CsA groups, even if fully attributable to the difference in CsA% instead of the confounding increase in castor oil %, is small enough to be caused by chance variation and sampling error. Further, errors of this size are to be expected from a study with such small sample sizes per treatment group. Ex. 1015 at 970 Table 1 (17 and 18 patients, respectively, in the corresponding 0.05% CsA and 0.10% CsA subgroups with moderate-to-severe dry eye disease).

151. Schiffman's Exhibit 1C (which is the same as that presented in Attar's Exhibit 2B), reproduced below, similarly failed to establish any statistically significant difference between the tested emulsions because it does not present the raw values of CsA measured in the eye tissues. Prior to the submission of the Allergan declarations, it was known that the minimal therapeutic levels of CsA in ocular tissues was 50 to 300 ng/mL. Ex. 1011. Instead of comparing the results to the threshold for therapeutic efficacy, Schiffman Exhibit 1C arbitrarily compares it to the level observed with 0.10% CsA in a 1.25% castor oil emulsion. Moreover, because Exhibit 1C reports no raw values for CsA measured in the eye tissue, it is entirely possible that all emulsions satisfy the concentration threshold for therapeutic efficacy, and that any increased delivery is immaterial. In other words, depending on the raw values involved, Exhibit 1C may be highlighting a distinction without a difference. Because Exhibit 1C lacks raw CsA values and error measurements, no meaningful conclusion can be derived from the bar graphs presented therein, nor can a statistically significant increase in therapeutic potential be derived.

Schiffman Declaration Exhibit C



Ex. 1004 at 0224.

152. Moreover, as discussed in greater detail with respect to claims 1, 18, and 23 in Ground 1, the teachings of Sall in combination with Ding '979 pointed to the 1.25% castor oil vehicle as the only vehicle in Ding '979's capable of making both the 0.05% CsA and 0.10% CsA emulsions having CsA-castor oil ratios that were within the "more preferred" range and within the ratio range disclosed in Example 1. *See, e.g.*, ¶ 107 above. Thus, applicants' assertions that it was surprising and unexpected in view of the prior art that the 0.05% CsA in 1.25% castor oil emulsion provided superior results fails to properly account for the teachings of Ding '979 in view of Sall.

XI. CONCLUDING STATEMENTS

153. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be

subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

154. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: May 12, 2016

By: / Mansoor Amiji /
Mansoor Amiji, PhD

XII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 8,633,162 to Acheampong <i>et al.</i>
1003	<i>Curriculum Vitae</i> of Dr. Mansoor Amiji
1004	File history of 8,633,162 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 OPTHALMOLOGY 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</i> , 2 LACRIMAL GLAND, TEAR FILM, AND DRY EYE SYNDROMES 1001 (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 TRANSPL. PROC. 650 (1988)
1012	K. Kunert <i>et al.</i> , <i>Analysis of Topical Cyclosporine Treatment of Patients with Dry Eye Syndrome</i> 118 ARCH OPHTHALMOL 1489 (2000)
1013	<i>Medications for Dry Eye</i> (1999) In PHYSICIANS' DESK REFERENCE FOR OPTHALMOLOGY (27th ed.) Montvale, NJ: PDR Network
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 OPTHALMOL. 967 (2000)
1016	REMINGTON'S 20 TH EDITION: THE SCIENCE AND PRACTICE OF PHARMACY (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 OPTHALMOL. 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 MED. INFLAMM. 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. OC. PHARM. THERAP. 411 (2002)
1022	STEDMAN'S MEDICAL DICTIONARY 27 TH EDITION (M.B. Pugh ed. 2000)