IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
MARSHALL DIVISION

ALLERGAN, INC., and THE SAINT REGIS MOHAWK TRIBE, *Plaintiffs*, v. TEVA PHARMACEUTICALS USA, INC., et al., *Defendants*.	§ § § § § § § § § § §	Case No. 2:15-cv-1455-WCB

FINDINGS OF FACT AND CONCLUSIONS OF LAW

BACKGROUND

The dispute in this Hatch-Waxman Act case relates to a condition known as "dry eye" and a pharmaceutical product known as "Restasis" that is intended to address that condition. Restasis is an emulsion consisting of various components, including the active ingredient cyclosporin A, an immunosuppressant, which is dissolved in castor oil, a fatty acid glyceride. Restasis, which is manufactured by plaintiff Allergan, Inc., is protected by six related patents, which will be referred to as "the Restasis patents." [1]

The defendants, Teva Pharmaceuticals USA, Inc.; Akorn, Inc.; Mylan, Inc.; and Mylan Pharmaceuticals, Inc., are generic drug manufacturers that wish to manufacture and sell

[1] Following the trial in this case, Allergan assigned all six of the Restasis patents to the Saint Regis Mohawk Tribe and received an exclusive license to the patents from the Tribe. Allergan subsequently moved to join the Tribe as a co-plaintiff. In a separate order entered today, the Court has granted that motion and added the Tribe as a plaintiff.

bioequivalent drugs having the same components as Restasis. Their principal contention is that the claims asserted by Allergan are invalid.

I. "Dry Eye" and KCS

Dry eye is a progressive condition that afflicts a substantial number of ophthalmic patients. It can cause great discomfort and sometimes leads to serious complications that can threaten the patient's eyesight. Dkt. No. 469, Trial Tr. 21; Dkt. No. 471, Trial Tr. 87-90.

In normal individuals, tears are produced naturally by the lacrimal glands above the eyes and accessory lacrimal glands in the eyelids. Dkt. No. 469, Trial Tr. 24-27. The tears form a film that covers the surface of the eye, providing protection to the eye and a smooth optical surface. The tear film in a normal individual consists of three distinct layers. The innermost layer is a mucus layer that rests directly on the cornea (the clear outer surface of the eye covering the iris and the pupil) and the conjunctiva (the tissue covering the white of the eye and lining the inside of the eyelids). The mucus layer assists the tear film in adhering to the surface of the eye. The second layer is an aqueous layer containing the tears. The topmost layer is a lipid layer produced by meibomian glands in the eyelid. The lipid layer impedes evaporation of the water from the tear film. In a normal individual, tears are produced continuously by the lacrimal and accessory lacrimal glands. The tears replenish the aqueous layer of the tear film, and then drain though tear ducts that discharge into the interior of the nose. Dkt. No. 469, Trial Tr. 24; Dkt. No. 473, Trial Tr. 32, 44.

Natural tearing serves important purposes, including providing nutrients and anti-bacterial agents to the surface of the eye and cleaning the ocular surface. The tear film also serves the important purpose of protecting the corneal and conjunctival epithelium, a thin layer of cells on the surface of the cornea and the conjunctiva. When natural tearing is inadequate (a

condition known as "aqueous-deficient dry eye"), or when the tear layer evaporates too quickly (a condition known as "evaporative dry eye"), the protective tear layer on top of the epithelium cells can be compromised, resulting in the exposure of those cells and causing damage that can be painful and can lead to adverse effects on vision. Dkt. No. 469, Trial Tr. 24-25; Dkt. No. 473, Trial Tr. 34-35. Individuals may suffer from aqueous-deficient dry eye, evaporative dry eye, or a mixture of both. Dkt. No. 473, Trial Tr. 40. The symptoms of dry eye can include a sandy or gritty feeling in the eyes, blurred vision, and infection. See U.S. Patent No. 5,981,607, col. 1, ll. 25-48.

Dry eye can be triggered by a variety of conditions. Sometimes, dry eye is caused by inflammation of the lacrimal glands or inflammation on the surface of the eye that interferes with nerve signals that would normally cause the lacrimal glands to produce tears. Dkt. No. 469, Trial Tr. 21-22, 26; see also Dkt. No. 473, Trial Tr. 34-35, 40. The condition in which dry eye is associated with inflammation and involves a deficiency in aqueous tear production is generally referred to as keratoconjunctivitis sicca ("KCS").[2] Dkt. No. 471, Trial Tr. 86-88. Evaporative dry eye can be caused by inadequate production of oil from the glands that normally replenish the lipid layer of the tear film. In a normal individual, oil in the lipid layer impedes the evaporation of tears from the surface of the eye. Dkt. No. 473, Trial Tr. 34-35, 44.

Ophthalmologists have used a variety of techniques to treat dry eye and KCS, but none has proved ideal. Frequently, ophthalmologists recommend that patients with mild to moderate

[2] Terminology used in this field is inconsistent in various respects. In particular, different authorities define KCS differently. The Court will use the definition used in the common specification and adopted by the Court at claim construction, which is consistent with what seems to be the prevailing view among ophthalmologists today. See U.S. Patent No. 8,629,111 ("the '111 patent"), col. 2, line 63, through col. 3, line 5; Dkt. No. 214, at 3-13.

dry eye use artificial tears several times a day. Dkt. No. 469, Trial Tr. 29-30. While artificial tears provide some temporary palliative relief, they do not address the underlying conditions that cause dry eye. Other pharmaceutical treatments include corticosteroids, which address the inflammation that is often associated with dry eye, but have serious potential side effects that make long-term use problematical. Id. at 30-31; Dkt. No. 475, Trial Tr. 60-61. Non-pharmaceutical treatments have been employed, such as the use of "punctal plugs," which block the tear ducts and prevent tears from draining from the eye, thereby retaining naturally produced tears in the eye for a longer period of time; those devices, however, also come with undesirable side effects. Dkt. No. 469, Trial Tr. 30.

The evidence at trial described several common methods for diagnosing dry eye and KCS as well as methods for testing whether particular treatment regimens are effective. One commonly used diagnostic device is the Schirmer tear test. That test entails placing the end of a strip of filter paper under the patient's eyelid and measuring how many millimeters of the paper are wetted by the patient's tears within five minutes. Wetting of less than a certain amount, such as 10 millimeters on the strip, is indicative of an abnormally low amount of tear production. The Schirmer tear test can be conducted either with or without an ocular anesthetic. Conducting the test with anesthesia is considered a better test of baseline tearing, i.e., the tearing that occurs continuously and naturally in the absence of any unusual stimulation. Conducting the test without anesthesia provides a measure of baseline tearing plus "reflexive tearing," i.e., tearing that results in response to a stimulus such as an irritant in the eye, because the irritation of the paper under the eyelid tends to provoke more tearing. Dkt. No. 469, Trial Tr. 28-30. There is significant variability in Schirmer test scores depending on the circumstances in which the test is conducted, which makes assessment of those scores challenging. Dkt. No. 475, Trial Tr. 131-32.

Another commonly used diagnostic device is corneal and conjunctival staining, in which a stain is placed in the eye. Particular stains can be used that highlight dry areas on the surface of the eye or rough areas of the cornea, thus allowing the ophthalmologist to measure the degree of the patient's dry eye problem and identify areas of the cornea that have been damaged by dry eye conditions. Dkt. No. 469, Trial Tr. 26. "Rose bengal" conjunctival staining is a method to test for drying and damage to the surface of the eye and shows devitalized areas of the conjunctiva. Dkt. No. 470, Trial Tr. 72; Dkt. No. 472, Trial Tr. 25; Dkt. No. 473, Trial Tr. 37. "Fluorescein" corneal staining shows areas of superficial punctate keratitis, also known as punctate epithelial keratopathy, i.e., epithelial defects in which the outer layer of the cornea has been damaged or lost. Fluorescein staining can also be used to detect "tear break-up time," i.e., the time it takes for dry spots to appear in the tear film. Dkt. No. 469, Trial Tr. 25; Dkt. No. 473, Trial Tr. 37; Dkt. No. 474, Trial Tr. 15. Other measures of the existence of and severity of dry eye include subjective measures, such as overall discomfort levels reported by patients and specific types of discomfort, such as a sandy or gritty feeling, ocular dryness, photophobia, or a burning or stinging sensation.

II. The Development of Restasis

Allergan specializes in the development and sale of ophthalmic drugs, among other products. One of Allergan's long-term projects has been to develop products effective to treat dry eye and its symptoms. For some time, Allergan has manufactured and sold artificial tears, and in 2002, it began selling a product, Refresh Endura, that used a formulation consisting of artificial tears with 2.5% by weight castor oil added to the formulation. That product was designed to have enhanced benefits for persons suffering from dry eye or KCS, but it was not a

commercial success. Dkt. No. 473, Trial Tr. 43, 88; Dkt. No. 475, Trial Tr. 174; Dkt. No. 476, Trial Tr. 12.

In the 1990s, Allergan began conducting research using combinations of castor oil and an immunosuppressant known as cyclosporin A.[3] Allergan's cyclosporin research program began in earnest in 1993 when Allergan licensed from Sandoz, Inc., the technology of treating aqueous-deficient dry eye with cyclosporin. That technology was the subject of U.S. Patent No. 4,839,342 to Kaswan ("the '342 patent" or "the Kaswan patent"). The Kaswan patent, which is prior art to the Restasis patents, claimed methods for enhancing or restoring lacrimal gland tearing comprising topically administering cyclosporin to the eye in a pharmaceutically acceptable vehicle. '342 patent, col. 9, ll. 19-22. Topical administration, the Kaswan patent disclosed, provides a way to direct the cyclosporin to the target tissues "without the accompanying high risk of adverse responses and high cost associated with systemic treatments." Id., col. 5, ll. 15-25.

Kaswan disclosed the use of cyclosporin "in any efficacious concentrations, e.g., 0.01 to saturation (e.g., greater than 20 weight percent)." '342 patent, col. 5, ll. 56-59. The preferred concentration of cyclosporin, according to Kaswan, was from 0.1% to 20% by weight. Id., col. 5, ll. 59-61; id., col. 6, ll. 21-26. The Kaswan patent also recited the use of castor oil, among other compounds, as a pharmaceutically acceptable vehicle for delivering cyclosporin to the eye. Id., col. 9, ll. 34-38; id., col. 10, ll. 18-22, 36-40.

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[3] Cyclosporin A is sometimes spelled "cyclosporine" to distinguish it from other cyclosporins, such as cyclosporins B, C, and D. See U.S. Pat. No. 4,839,342, col. 3, ll. 7-11. The parties in this case, however, have referred to cyclosporin A as simply "cyclosporin" or "CsA." The Court will follow that convention.

One of the major problems with using cyclosporin to treat dry eye is that cyclosporin is highly insoluble in water and is therefore very difficult to deliver in an aqueous solution. For that reason, formulating an appropriate vehicle for delivering cyclosporin to the eye posed a difficult challenge. Allergan was able to solve that problem by formulating an oil-in-water emulsion that contained a small amount of castor oil (a hydrophobic vehicle that would dissolve the cyclosporin), together with an emulsifier and an emulsion stabilizer in water. That approach allowed small droplets of the cyclosporin/castor oil solution to be suspended in an emulsion from which the cyclosporin would be available to the target tissue. In addition, the emulsion stabilizer was able to keep the emulsion stable for long periods of time. Allergan's work on cyclosporin/castor oil emulsions is disclosed and claimed in two Allergan patents, both of which are prior art to the Restasis patents.

The first of those two patents is U.S. Patent No. 5,474,979 ("the '979 patent" or "the Ding I patent"), which issued in 1995 and expired in 2014. That patent is entitled "Nonirritating Emulsions for Sensitive Tissue." The '979 patent disclosed and claimed a pharmaceutical emulsion consisting of between about 0.05% and about 0.4% by weight cyclosporin; between about 0.625% and about 0.4% by weight castor oil; about 1% by weight polysorbate 80 (an emulsifier); about 0.05% by weight Pemulen (an emulsion stabilizer); and about 2.2% by weight glycerin. The rest of the emulsion consisted of water and an amount of sodium hydroxide sufficient to adjust the pH to between about 7.2 and 7.6. Ding I patent, col. 6, ll. 21-42. The resulting emulsion was found to be suitable for topical application to ocular tissue.

The Ding I patent described the disclosed cyclosporin/castor oil emulsion as having a "high comfort level and low irritation potential," Ding I patent, col. 1, ll. 8-9, as well as long-term stability, id., col. 3, ll. 58-63. The emulsion was tested in rabbits and was determined to

have both therapeutic efficacy and low toxicity. Id., col. 5, ll. 10-28. The Ding I patent contained four examples, the first two of which contained multiple formulations drawn from the disclosed and claimed ranges of components. The individual embodiments in Example 1 included amounts of cyclosporin varying between 0.05% and 0.4%, and amounts of castor oil varying between 0.625% and 5%. Example 1D in the Ding I patent contained 0.1% cyclosporin and 1.25% castor oil, while Example 1E contained 0.05% cyclosporin and 0.625% castor oil.

Example 1

	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., col. 4, ll. 31-43. Thus, Example 1D contained the same amount of castor oil as found in Restasis (but twice as much cyclosporin), while Example 1E contained the same amount of cyclosporin as found in Restasis (but half as much castor oil).

All of the embodiments in Example 1 of the Ding I patent had a cyclosporin-to-castor oil ratio of 0.08, except for Example 1B, which had a cyclosporin-to-castor oil ratio of 0.04 (the same ratio as in Restasis). The Ding I patent stated that the preferred weight ratio of cyclosporin to castor oil was below 0.16 (which is the maximum solubility level of cyclosporin in castor oil), and that the more preferred weight ratio of cyclosporin to castor oil was between 0.02 and 0.12. Ding I patent, col. 3, ll. 15-20.

The Ding I patent stated that the formulations in Examples 1A through 1D were tested for ocular bioavailability in rabbits, and that "a therapeutic level of cyclosporin was found in the

tissues of interest after dosage." Ding I patent, col. 5, ll. 18-25. No difference in toxicity was found between the tested cyclosporin formulations (Examples 1A through 1D) and formulations without cyclosporin. Id., col. 5, ll. 26-28. All five example cyclosporin formulations (Examples 1A through 1E) showed long-term stability. Id., col. 5, ll. 29-30. For Examples 1A through 1D, no crystallization of the cyclosporin was detected after nine months at room temperature. Id., col. 5, ll. 30-32.

The second of the two Allergan patents relating to ocular emulsions is the prior art U.S. Patent No. 5,981,607 ("the '607 patent" or "the Ding II patent"), which is entitled "Emulsion Eye Drop for Alleviation of Dry Eye Related Symptoms in Dry Eye Patients and/or Contact Lens Wearers." The Ding II patent disclosed and claimed a method for alleviating dry eye related symptoms by topically applying to ocular tissue an emulsion of a higher fatty acid glyceride, polysorbate 80, and an emulsion-stabilizing amount of Pemulen in water, all without cyclosporin. Ding II patent, col. 9, ll. 2-7. One of the dependent claims of that patent recited the claimed emulsion in which the higher fatty acid glyceride was castor oil, in an amount between about 0.625% by weight and about 5% by weight; polysorbate 80 was present in an amount of about 1% by weight; the ratio of the castor oil to the polysorbate 80 was between about 0.3 to about 30; Pemulen was present in an amount of about 0.05% by weight; and glycerine was present in an amount of about 2.2% by weight. Id., col. 10, ll. 4-10.

The Ding II patent noted that, unlike palliative agents such as artificial tears, "therapeutic treatments directed at the underlying inflammatory process may prove beneficial in correcting the underlying disorder." Ding II patent, col. 1, ll. 56-61. The Ding II patent also noted that the lipid layer of the tear film is believed to be responsible for retarding evaporation of water from the tear film. If the lipid layer of the tear film is disturbed, "excessive evaporation of water from

the eye may occur, leaving the surface of the eye 'dry.'" Id., col. 2, ll. 9-17. The Ding II patent stated that the disclosed and claimed emulsion, which contains a higher fatty acid glyceride—and castor oil in particular—"provides for long retention of the fatty acid glyceride when the emulsion is instilled into an eye. This in turn can retard water evaporation from the eye which alleviates dry eye symptoms." Id., col. 3, line 66, through col. 4, line 3.

III. Clinical Studies and the FDA Application

In the late 1990s, with the hope of obtaining approval of a cyclosporin/castor oil pharmaceutical from the U.S. Food and Drug Administration ("FDA"), Allergan conducted two phases of clinical trials of cyclosporin/castor oil emulsions of the sort disclosed in the two Ding patents. In the first clinical trial, referred to as the "Phase 2" study, Allergan tested several combinations of the castor oil and cyclosporin components—0.05% cyclosporin with 0.625% castor oil; 0.1% cyclosporin with 1.25% castor oil; 0.2% cyclosporin with 2.5% castor oil; and 0.4% cyclosporin with 5% castor oil. Those formulations were the same as the formulations set forth in Examples 1A, 1C, 1D, and 1E in the Ding I patent. Also tested in the Phase 2 study was a vehicle—a solution containing 2.5% castor oil with no cyclosporin.

As is commonly the case, the Phase 2 testing was a smaller "dose-ranging" trial designed to determine the effectiveness and safety of particular doses of the drug, so as to enable the researchers to settle on an appropriate dosage level for subsequent large-scale Phase 3 clinical studies. Those Phase 3 studies would be used to support an application to the FDA for permission to market a cyclosporin/castor oil emulsion as a new drug for treating dry eye and KCS. Dkt. No. 469, Trial Tr. 32-34.

Allergan's Phase 2 study was reported in a journal article, Dara Stevenson et al., Efficacy and Safety of Cyclosporin A Ophthalmic Emulsion in the Treatment of Moderate-to-severe Dry

Eye Disease, A Dose-Ranging, Randomized Trial, 107 Ophthalmology 967 (May 2000), DTX-1018. The Stevenson paper reported that 88 patients with moderate-to-severe dry eye disease completed the study—16 in the castor-oil-only vehicle, or control, group; 17 in the 0.05% group; 18 in the 0.1% group; 20 in the 0.2% group; and 17 in the 0.4% group. Id. at 970. Stevenson revealed the concentration of cyclosporin in each tested formulation. Stevenson did not disclose the percentage of castor oil in each formulation, but it disclosed that the amount of castor oil increased relative to the increase in cyclosporin in each formulation so that all of the cyclosporin would be dissolved. Id. at 968.

The conclusion reached by Stevenson was that the treatment with topical cyclosporin at all tested concentrations significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease, and that those improvements resulted in a significant decrease in the effect of the disease on vision-related functioning. DTX-1018, at 972. That result, according to Stevenson, was consistent with earlier studies regarding the use of topical cyclosporin to treat dry eye disease and Sjögren's syndrome, a systemic autoimmune disease that is characterized by severe dry eye. Id. at 972-73; see also Dkt. No. 469, Trial Tr. 54.

All of the combinations containing cyclosporin proved safe and effective in increasing tearing in certain patient test groups, and all outperformed the castor-oil-only vehicle. Stevenson added, however, that it was "important to note that the vehicle emulsion used in [the Phase 2] study performed well on its own, producing significant improvement from baseline [(i.e., the patients' pre-treatment condition)] in several parameters." DTX-1018, at 973. One of the factors contributing to the beneficial effects of the castor-oil-only vehicle, according to Stevenson, "may be its sustained residence time on the ocular surface," which was three to four

hours. Id. The lengthy residence time, Stevenson suggested, "may help reduce evaporation of the limited volume of natural tears present in patients with dry eyes." Id.

With respect to safety, Stevenson reported that few adverse effects—and no serious adverse effects—were reported among the trial participants. DTX-1018, at 973. Stevenson noted that blood analysis showed that even the formulation with the highest concentration of cyclosporin resulted in minimal systemic absorption of cyclosporin. Id. Stevenson also reported that the formulations were all well tolerated by patients, and that there were no complaints of ocular discomfort, burning, or itching. Id.

As for comparative results, Stevenson concluded that there was no clear dose-response relationship between the 0.05% cyclosporin formulation and the formulations containing greater amounts of cyclosporin (i.e., efficacy did not increase with increases in dosage amounts). Nonetheless, differences were detected in the performance of the different formulations as to particular efficacy measures. Stevenson concluded that the 0.1% cyclosporin formulation "produced the most consistent improvement in objective and subjective endpoints (such as superficial punctate keratitis and rose bengal staining)," while the 0.05% cyclosporin formulation "produced the most consistent improvements in patient symptoms (such as sandy/gritty feeling and ocular dryness)." DTX-1018, at 974. The fact that the higher concentrations of cyclosporin did not show any additional therapeutic benefit with increased concentration, Stevenson noted, "suggests that subsequent clinical studies should focus on the cyclosporin 0.05% and 0.1% formulations." Id.

Following the Phase 2 study, Allergan proceeded to what is known as the Phase 3 studies. Initially, Allergan proposed in Phase 3 to test only the formulation containing 0.1% cyclosporin and 1.25% castor oil against its vehicle (i.e., 1.25% castor oil with no cyclosporin). Allergan

elected that course of action based on its assessment that the 0.1% cyclosporin formulation had done best in the Phase 2 study. However, after considering the same Phase 2 data, the FDA wanted Allergan to test the lower dose of cyclosporin—the 0.05% dosage. So Allergan agreed to add the 0.05% dosage level to the Phase 3 trials, but with a castor oil concentration of 1.25%, the same as that used in the 0.1% cyclosporin formulation and the castor-oil-only vehicle. Dkt. No. 470, Trial Tr. 76-84.

Two separate Phase 3 trials were conducted simultaneously. A total of 671 patients completed the two Phase 3 trials—235 in the 0.05% cyclosporin group, 218 in the cyclosporin 0.1% group, and 218 in the castor-oil-only vehicle group. Each tested formulation contained 1.25% castor oil, and each formulation also contained 1% polysorbate 80, 0.05% Pemulen, and 2.2% glycerin.

Like the Phase 2 study, the Phase 3 studies were the subjects of a published journal article, which is also prior art in this case. See Kenneth Sall et al., Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, 107 Ophthalmology 631 (April 2000), DTX-1017A. The Sall paper revealed the percentages of cyclosporin used in each formulation. Like Stevenson, Sall did not expressly reveal the percentage of castor oil used in the formulations.[4]

Sall explained that the purpose of the two Phase 3 trials was to compare the efficacy and safety of the cyclosporin 0.05% and 0.1% formulations to the vehicle in patients with moderate

[4] Stevenson did not specify that the oil used in the formulations in the Phase 2 study was castor oil, but Sall revealed that the study reported in Stevenson used castor oil. See DTX-1017A, at 632 ("The doses of [cyclosporin A] used were based on the results of an earlier dose-ranging study [citing Stevenson]. Both the [cyclosporin A] emulsions and vehicle were sterile, nonpreserved castor oil in water emulsions . . . .").

to severe dry eye disease. DTX-1017A, at 631. According to Sall, the Phase 3 studies showed that both cyclosporin formulations produced significantly better results than the vehicle alone, and that the 0.05% treatment gave significantly greater improvements, as compared to vehicle, in three subjective measures of dry eye disease (blurred vision, the need for artificial tears, and the physician's evaluation of the patient's global response to treatment) for at least some time points. Id. at 631, 637. Sall also reported no dose-response effect between the 0.05% cyclosporin/1.25% castor oil formulation and the 0.1% cyclosporin/1.25% castor oil formulation, and that both of the cyclosporin treatments exhibited excellent safety profiles. Id.

Sall stated that there was a statistically significant improvement in the corneal staining scores for all three test groups compared to the patients' baseline scores. In addition, Sall reported statistically significant improvement in the 0.05% cyclosporin group compared to the castor-oil-only vehicle for corneal staining at months 4 and 6. DTX-1017A, at 635.

The study reviewed data from the patients' follow-up physician visits at various points in the course of the trials. At three months into the trials, there was a statistically significant difference between the 0.05% cyclosporin group and the patients' baseline scores on the categorized Schirmer tear test with anesthesia; and at six months, both the 0.05% cyclosporin group and the 0.1% cyclosporin group showed statistically significant improvements compared to the patients' baseline scores on that test.[5] Sall also reported that at month 3 there was a statistically significant difference between the 0.05% cyclosporin group and the vehicle group, but not a statistically significant difference between the 0.05% cyclosporin group and the 0.1%

[5] The "categorized" Schirmer tear test places the Schirmer scores derived from the test into five categories, ranging from category 1 (0-3 millimeters of wetness on the filter paper) to category 5 (more than 14 millimeters of wetness). DTX-1018, at 635.

cyclosporin group. As for the categorized Schirmer tear tests without anesthesia, the two cyclosporin formulation groups showed statistically significant improvements over the baseline, but there was no statistically significant difference between the two cyclosporin groups. DTX-1017A, at 635-36.

With respect to the subjective ocular symptoms, Sall reported that the decrease in blurred vision from the patients' baseline scores was statistically significant for both cyclosporin groups at all follow-up visits. For the castor-oil-only vehicle, however, the decrease was statistically significant only at the six-month visit. The improvement in blurred vision was also significantly greater for the 0.05% group as compared to the vehicle group at all follow-up visits. DTX-1017A, at 636.

Similarly, statistically significant changes from baseline were observed within all treatment groups at all points with regard to dryness, sandy/gritty feeling, itching, burning and stinging, and pain. However, there were no statistically significant among-group differences with regard to any of those variables.[6] DTX-1017A, at 636. There were also statistically significant decreases in the use of artificial tears in the treatment groups compared to baseline, but no statistically significant differences among the treatment groups as to that variable. Id.

With respect to the physicians' subjective assessment of the global response to treatment, Sall reported that the 0.05% and 0.1% cyclosporin groups showed an improvement over the patients' baseline and somewhat better results than the castor-oil-only vehicle group. The

[6] An among-group analysis determines whether any one of the groups—vehicle or treatment—has results that are significantly different from the rest of the groups. If there are no statistically significant among-group differences, there will be no statistical significance in any pair-wise comparisons between any two of those groups. See Dkt. No. 469, Trial Tr. 59.

improvements seen in the two cyclosporin groups, however, were very similar. See DTX-1017A, at 636.

> Sall concluded that the most important overall finding of the two Phase 3 trials
>
> 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 eye drops, and the physician's evaluation of global response to treatment).

DTX-1017A, at 637. Significantly, Sall also noted that the castor oil vehicle for the cyclosporin ophthalmic emulsion used in the two Phase 3 trials

> provided substantial palliative benefits, producing significant improvements from [the patients'] 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.

The assessment of the Phase 3 results, as compared to the Phase 2 results, is a matter of intense dispute in this case. Relying primarily on Stevenson, Allergan contends that the Phase 2 study showed significantly better results for the 0.1% cyclosporin formulation compared to the 0.05% cyclosporin formulation. Allergan also contends that the Phase 3 trials showed significantly better results for the 0.05% cyclosporin formulation compared to the 0.1% cyclosporin formulation. The superior performance of the 0.05% formulation in the Phase 3 trials, according to Allergan, was unexpected, particularly in light of the fact that the 0.05% formulation in the Phase 3 studies contained twice the concentration of castor oil (1.25% castor oil) as the 0.05% formulation in the Phase 2 study (0.625% castor oil). The purportedly superior

performance of the 0.05% formulation is the principal basis for Allergan's contention that the 0.05% formulation was patentable over the Ding I reference, even though each of the components of the 0.05% formulation fell within the range of the components disclosed and claimed in Ding I.

The defendants contend that there was no statistically significant difference between the 0.05% cyclosporin formulation and the 0.1% formulation in the Phase 2 study. The defendants also point out that while both of the cyclosporin formulations did better than the castor-oil-only vehicle formulation in the Phase 3 studies, there was no overall statistically significant difference between the 0.05% cyclosporin formulation and the 0.1% formulation in those trials. Accordingly, the defendants contend, there has been no showing that the 0.05% formulation performed in a way that was unexpected, so as to render the 0.05% formulation patentable over Ding I.

Following the Phase 3 study, Allergan filed a New Drug Application ("NDA") with the FDA seeking authorization to market the 0.05% cyclosporin product that was tested in the Phase 3 trials. The proposed commercial product, which is Restasis, would contain all of the components of the Phase 3 0.05% cyclosporin formulation, including 1.25% castor oil. The FDA approved the application, authorizing the sale of Restasis for the following indication: "Restasis is a topical immunomodulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs." Dkt. No. 469, Trial Tr. 64; PTX-32. Since its launch in 2003, Restasis has been a highly successful product for Allergan.

IV. The Prosecution of the Restasis Patents

Over the 10-year period following the approval of Allergan's NDA for Restasis, Allergan continued to prosecute applications for cyclosporin/castor oil formulations before the Patent and Trademark Office ("PTO"), albeit in a rather desultory fashion. Allergan first filed provisional application No. 60/503,137 on September 15, 2003, followed by U.S. Patent Application No. 10/927,857 ("the '857 application"), which was filed on August 27, 2004. Those applications were directed to methods and compositions for treating the eye by administering a composition in the form of an emulsion comprising a hydrophobic component and a cyclosporin component in a therapeutically effective amount of less than 0.1% by weight, the weight ratio of the cyclosporin component to the hydrophobic component being less than 0.08. Dependent claims in the application recited the hydrophobic component in an amount greater than 0.625% of the composition and the hydrophobic component comprising castor oil.

Allergan withdrew a number of the claims of that application, and the examiner rejected the remaining claims based in part on obviousness in light of the Ding I patent. The examiner concluded that it would have been obvious to modify the composition of Ding I by increasing the amount of castor oil from the amount found in Example 1D of the Ding I patent in order to reduce the ratio of the cyclosporin component to the hydrophobic component from 0.08, since Ding I claimed ratios as low as 0.02 and amounts of castor oil ranging from 0.625% to 5%. Application No. 10/927,857, Office Action Summary (Jan. 17, 2007), at 13-14. Allergan amended the application to include a claim to an emulsion comprising water, 1.25% castor oil, and 0.05% cyclosporin, which is the percentage of those components in Restasis. Application No. 10/927857, Amendment A (Mar. 27, 2007), at 10. The examiner again rejected the claims, and Allergan filed an appeal from the examiner's rejections.

In August 2007, while those proceedings were pending, Allergan filed a continuation of the '857 application, U.S. Patent Application No. 11/897,177 ("the '177 application"). The '177 application was similar to the '857 application, but it added claims regarding new conditions that the method was asserted to treat, including corneal graft rejection. Application No. 11/897,177, Methods of Providing Therapeutic Effects Using Cyclosporin Components (Aug. 28, 2007).

In June 2009, Allergan made a significant filing in both pending applications. Contrary to its previous assertions to the PTO, Allergan made the following concession with respect to the '857 application:

> The applicants concede that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at Composition II of the present application. The differences are insignificant. 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 1.25% (0.05% / 1.25% = 0.04). The applicants concede that in making this selection (0.05% cyclosporin and 1.25% 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 teaching of the Ding reference, and the Office should disregard any statements by the applicants suggesting otherwise, whether in this application or in co-pending application no. 11/897,177.

DTX-1291A, at 481. "Composition II" is the Restasis formulation. Allergan made a similar concession with respect to the '177 application. Application No. 11/897,177, Amendment (June 15, 2009), at 7-8.

In the prosecution of the '857 application, Allergan then filed a request for continued examination. It withdrew its pending appeal of the previous rejection, canceled all of the previous claims in the application, and added a new claim to a composition in which the amount

of cyclosporin is less than 0.05% and the ratio of cyclosporin to castor oil is less than 0.04. DTX-1291A, at 476-77. The examiner rejected that claim as obvious in light of the Ding I patent and for non-statutory double patenting over Ding I. See Application No. 10/927,857, Office Action Summary (Sept. 1, 2009).

The examiner subsequently issued a notice of abandonment with respect to the '857 application. Application No. 10/927,857, Notice of Abandonment (Apr. 11, 2011). The '177 application ultimately issued as U.S. Patent No. 8,618,064, but only for the treatment of corneal graft rejection.

In August 2013, shortly before the Ding I patent expired, and while the '177 application was still pending, Allergan filed a series of new continuation applications, all deriving, directly or indirectly, from the '177 application. See PTO Docket No. 17618CON6 (AP), Preliminary Amendment (Aug. 7, 2013); PTO Docket No. 17628CON2B (AP), Preliminary Amendment (Aug. 14, 2013); PTO Docket No. 17628CON5B (AP), Preliminary Amendment (Aug. 14, 2013); PTO Docket No. 17618CON6B (AP), Preliminary Amendment (Aug. 14, 2013); PTO Docket No. 17628CON7B (AP), Preliminary Amendment (Aug. 14, 2013); PTO Docket No. 17628CON6CON1 (AP), Preliminary Amendment (Mar. 21, 2014). The amendments made a change in the specification for three of the applications, adding four sentences further describing the role of cyclosporin as an immunosuppressant and the conditions that can be treated with cyclosporin. Four of the new applications became the four patents at issue in this lawsuit. The new applications were intended to protect the Restasis composition and the method of using that composition in treating dry eye and KCS after the expiration of the Ding I patent in 2014.

At the outset of the prosecution of the 2013 applications, Allergan withdrew its previous concessions that the claims of the '857 and '177 applications would have been obvious in light of

the Ding I patent. With respect to the June 2009 concessions of obviousness in those two applications, Allergan stated in each of the 2013 applications that "since these comments have been filed, the Applicants have collected evidence that supports the patentability of the pending claims." PTX-2D, at 7.

Shortly after filing the new applications, Allergan's patent counsel argued to the examiner that the claims in the new applications were patentable because of evidence of unexpected results, commercial success, and long-felt need. Application No. 13/967,163, Applicant-Initiated Interview Summary (Oct. 17, 2013), at 3. The examiner rejected the claims, once again relying heavily on the Ding I patent. PTX-2E, at 479-82.[7]

Responding to that rejection, Allergan's patent counsel submitted declarations from Dr. Rhett M. Schiffman and Dr. Mayssa Attar in an effort to show that the claimed formulation had produced new and unexpected results relative to the formulations set forth in Examples 1D and 1E in the Ding I patent. PTX-2A. The unexpected results, Allergan asserted, were related to two objective testing parameters for dry eye: Schirmer tear testing and decreases in corneal staining; and two subjective testing factors: blurred vision and the use of artificial tears.

In its written submission to the examiner, Allergan represented that Dr. Schiffman's declaration showed,

> surprisingly, the claimed formulation [of 0.05% cyclosporin and 1.25% castor oil] demonstrated an ***8-fold*** increase in relative efficacy for the Schirmer Tear Test score in the first study of Allergan's Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation discussed in Example 1E of Ding, tested in Phase 2 trials. The data presented herewith represents the subpopulation of Phase 2 patients with the same

[7] The discussion in the text relates to U.S. Patent Application No. 13/967,163, which became U.S. Patent No. 8,629,111, one of the six Restasis patents. The prosecution of the other co-pending applications, which became the other five Restasis patents, followed a similar course.

> reductions in tear production (x 5mm/5 min) as those enrolled in the Phase 3 studies. . . . Exhibits E and F also illustrate that the claimed formulations also demonstrated a *4-fold* improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a *4-fold* increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E). This was clearly a very surprising and unexpected result.

PTX-2F, at 543. Based on that submission and the accompanying declarations from Dr. Schiffman and Dr. Attar,[8] the examiner reversed course and allowed the claims. See PTX-2C. The examiner wrote that the Schiffman declaration

> is deemed sufficient to overcome the rejection of claims 37-61 based upon [Ding I] as set forth in the last Office action because: After carefully reviewing exhibits A-F, which compare the instantly claimed embodiment having 0.05%/1.25% castor oil with embodiments E and F of Ding et al. (0.10%/1.25% [cyclosporin/]castor oil and 0.05%/.625% cyclosporin/castor oil ratios), Examiner is persuaded that, unexpectedly, the claimed formulation (0.05% cyclosporin A/1.25% castor oil) demonstrated an 8-fold increase in relative efficacy for the Schirmer Tear Test score in the first study of Phase 3 trials compared to the relative efficacy for the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation disclosed in Example 1E of Ding, tested in Phase 2 trials. . . .
>
> Exhibits E and F also illustrate that the claimed formulations comprising 0.05% cyclosporin A/1.25% castor oil also demonstrated a 4-fold improvement in the relative efficacy for the Schirmer Tear Test score for the second study of Phase 3 and a 4-fold increase in relative efficacy for decrease in corneal staining score in both of the Phase 3 studies compared to the 0.05% by weight cyclosporin A/0.625% by weight castor oil formulation tested in Phase 2 and disclosed in Ding (Ding 1E).

Id. at 747-48. After making those findings, the examiner issued notices of allowance for all six Restasis patents, including the four patents at issue in this case.

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[8] Dr. Attar's declaration largely tracked the material in Dr. Schiffman's declaration, but it added that Allergan's pharmacokinetic testing on animal eyes showed that the amount of cyclosporin absorbed by the ocular tissues was higher for formulations that contained the same amount of cyclosporin but less castor oil, and that the amount of cyclosporin that reached the ocular tissues was greater for the 0.1% cyclosporin/1.25% castor oil formulation than for the 0.05% cyclosporin/1.25% castor oil formulation. Serial No. 13/961,828, Interview Summary, Preliminary Amendment, and Remarks (Dec. 5, 2013), at Ex. 2, ¶¶ 7-8.

V. The Restasis Patents

The six Restasis patents are U.S. Patent Nos. 8,629,111 ("the '111 patent"), 8,633,162 ("the '162 patent"), 8,642,556 ("the '556 patent"), 8,648,048 ("the '048 patent"), 8,685,930 ("the '930 patent"), and 9,248,191 ("the '191 patent"). Those patents contain a total of 157 claims, including both product and method claims. A limitation that is common to all of the claims (with slight variations in wording) is the formulation for Restasis, which is an 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." '111 patent, col. 16, ll. 20-29 (independent claim 18).

The specifications of the six Restasis patents are identical with only minor variations. The '111 specification is representative. It acknowledges that the use of cyclosporin to treat ophthalmic conditions is well known, as illustrated by the prior art Ding I patent and the Stevenson and Sall papers. The invention, according to the specification, is the use of an emulsion containing a hydrophobic component and a therapeutically effective cyclosporin component of less than 0.1%, in which the weight ratio of the cyclosporin component to the hydrophobic components is less than 0.08. '111 patent, col. 1, ll. 26-65; id., col. 2, ll. 28-34.[9]

The specification identifies higher fatty acid glycerides as "very useful," and specifies that "[e]xcellent results are obtained using a hydrophobic component comprising castor oil." '111 patent, col. 9, ll. 44-45, 51-52. The specification further states that it is believed that castor

[9] At one point, the '111 specification refers to the weight ratio of the cyclosporin component to the hydrophobic component as being "greater than 0.08," '111 patent, col. 9, ll. 20-21, but that appears to be a typographical error; "less than 0.08" appears to have been intended.

oil "includes a relatively high concentration of ricinoleic acid which itself may be useful in benefiting ocular tissue and/or providing one or more therapeutic effects when administered to the eye." Id., col. 9, ll. 53-57.

The specification refers to emulsifier components that are conventionally used and well known in the art, including polysorbate 80, one of the preferred emulsifiers. '111 patent, col. 10, ll. 24-39. In addition, the specification calls for the use of polyelectrolyte or emulsion stabilizing components. Id., col. 10, line 48, through col. 11, line 28. With respect to the emulsion stabilizing components, the specification states:

> One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and [is] commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

Id., col. 11, ll. 29-38.

The specification refers to two compositions, which were the two cyclosporin/castor oil compositions that were tested in the Phase 3 trials. The two compositions are denominated Composition I and Composition II. The specification reports that Composition II, which contains the claimed levels of 0.05% cyclosporin and 1.25% castor oil, "provides overall efficacy in treating dry eye disease substantially equal to that of Composition I," which contains 0.1% cyclosporin and 1.25% castor oil. '111 patent, col. 14, ll. 35-39. The specification then states that "[t]his is surprising for a number of reasons." Id., col. 14, line 40. First, the reduced concentration of cyclosporin in Composition II "would have been expected to result in reduced overall efficacy in treating dry eye disease." Id., col. 14, ll. 40-44. Second, the larger amount of

castor oil relative to the amount of cyclosporin in Composition II "might have been expected to cause increased eye irritation," but in fact both Composition I and Composition II were found to be substantially non-irritating. Id., col. 14, ll. 44-49. Using relatively greater amounts of castor oil, the specification adds, "is believed to take advantage of the benefits, for example the ocular lubrication benefits, of castor oil, as well as the presence of ricinoleic acid in the castor oil, to at least assist in treating dry eye syndrome" in combination with cyclosporin. Id., col. 14, ll. 50-56. In addition, the specification notes that relatively greater amounts of castor oil had the advantage of causing the emulsion to break down more quickly in the eye, so as to reduce vision distortion resulting from the presence of the emulsion in the eye. Id., col. 14, ll. 57-67. And the reduced amount of cyclosporin in Composition II, according to the specification, reduces the risk of undesirable side effects as compared to Composition I. Id., col. 15, ll. 1-8.

VI. The Hatch-Waxman Act and Allergan's Lawsuit

In 2015, Allergan filed this action under the Hatch-Waxman Act, the name commonly used to refer to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 96-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360(cc), 35 U.S.C. §§ 156, 271, 282), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066. Allergan alleged that all four defendants had infringed the Restasis patents under section 271(e)(2) of Title 35 by filing Abbreviated New Drug Applications ("ANDAs") for drugs bioequivalent to Restasis. Allergan also sought a declaratory judgment that the defendants' proposed sales of the bioequivalent drugs would infringe the Restasis patents under sections 271(a), (b), and (c) of Title 35. The defendants answered that the Restasis patents are invalid on several grounds, and that none of the defendants infringe the Restasis patents.

The Hatch-Waxman Act was intended to strike a balance between two competing policy interests: (1) to induce pioneering research and development of new drugs; and (2) to enable competitors to bring low-cost generic copies of those drugs to market if those drugs are not entitled to patent protection. See Andrx Pharms., Inc. v. Biovail Corp., 276 F.3d 1368, 1371 (Fed. Cir. 2002).

To promote those objectives, the Hatch-Waxman Act provides a means for pharmaceutical companies to resolve patent disputes relatively quickly. Ideally, it provides for a prompt determination of whether particular drugs made and sold by brand-name pharmaceutical companies are protected by valid patents. If the patents are held infringed and not invalid, the covered drugs cannot be made and sold by generic manufacturers until the patents expire. If the patents are held invalid or not infringed, the Act provides a mechanism for prompt approval of the generic versions of the drugs by the FDA, which allows the generic drugs to be made and sold.

In order to obtain the necessary FDA approval to market a new drug, a pharmaceutical company must file an NDA with the FDA. That application is designed to show the FDA, through rigorous testing procedures, that the drug is safe and effective for its proposed indications. After considering the application, and often after extended negotiations with the pharmaceutical company, the FDA may grant the application and authorize the company to market the drug for particular indications. The company is restricted to marketing the drug for those indications, as dictated by FDA regulations that govern both labeling and advertising for all prescription drugs. See 21 C.F.R. § 202.1 (advertising); id. § 201.1-201.327 (labeling).

In an effort to speed up the approval process for generic drugs, the Hatch-Waxman Act provides that a generic drug manufacturer may submit an ANDA for approval by the FDA.

Unlike an NDA, an ANDA may rely on the safety and efficacy studies previously submitted as part of the NDA. In order to take advantage of those studies, the ANDA applicant must demonstrate that the proposed generic drug is bioequivalent to the previously approved drug product. See 21 U.S.C. § 355(j)(2)(A); Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc., 527 F.3d 1278, 1282 (Fed. Cir. 2008).

Under the Hatch-Waxman Act, NDA holders are required to notify the FDA of all patents that "claim[] the drug for which the [NDA] applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C. § 355(b)(1), (c)(2). The FDA lists such patents in a publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," which is commonly referred to as the "Orange Book." See Bayer Schering Pharma AG v. Lupin, Ltd., 676 F.3d 1316, 1318 (Fed. Cir. 2012); AstraZeneca LP v. Apotex, Inc., 633 F.3d 1042, 1045 (Fed. Cir. 2010).

As part of the approval process for generic drugs, an ANDA applicant must make one of four certifications with respect to each patent listed in the Orange Book that pertains to the drug for which the ANDA applicant is seeking approval. Those certifications are (1) that no such patent information has been submitted to the FDA; (2) that the patent has expired; (3) that the patent is set to expire on a certain date; or (4) that the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA has been submitted. 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). Those certifications are known as paragraph I, II, III, or IV certifications. See Janssen Pharmaceutica, N.V. v. Apotex, Inc., 540 F.3d 1353, 1356 (Fed. Cir. 2008).

When a generic manufacturer files a paragraph IV certification as part of its ANDA, it must give notice to the patentee and the NDA holder. The notice must include a detailed

statement of the factual and legal bases for the opinion of the ANDA applicant that the patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug product. 21 U.S.C. § 355(j)(2)(B)(i); see Apotex, Inc. v. Thompson, 347 F.3d 1335, 1338 (Fed. Cir. 2003).

The Hatch-Waxman Act creates an "artificial" type of infringement that allows for the adjudication of the parties' rights in patents that are the subject of a paragraph IV certification. See Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 676 (1990); Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1351 (Fed. Cir. 2004). In particular, 35 U.S.C. § 271(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA for a drug claimed in a patent or the use of which is claimed in a patent if the purpose of the submission of the ANDA is to obtain approval to engage in the commercial manufacture, use, or sale of the drug claimed in the patent, or the use of which is claimed in the patent before the patent's expiration.

If the patentee files an infringement action within 45 days after receiving notice of the paragraph IV certification, an automatic stay of 30 months goes into effect, during which the FDA cannot approve the ANDA unless the suit is resolved or the patent expires. 21 U.S.C. § 355(j)(5)(B)(ii). If no infringement action is filed during the initial 45-day period after the paragraph IV certification, the FDA may approve the ANDA. Id. In addition, pursuant to a 2003 amendment to the Hatch-Waxman Act, if the patentee or NDA holder does not bring an infringement action within 45 days after receiving notice of a paragraph IV certification, the ANDA applicant may bring a civil action for a declaratory judgment that the patent at issue is invalid or will not be infringed by the drug for which the applicant seeks approval. Id. § 355(j)(5)(C).

In February 1999, Allergan filed an NDA for the drug that would become Restasis, containing 0.05% cyclosporin and 1.25% castor oil. The approval process took several years,

during which Allergan presented data showing that the Restasis formulation was safe and effective. In particular, Allergan submitted data showing that the Restasis formulation did not have significant side effects and demonstrated significant improvements over the vehicle in categorized Schirmer wetting scores at the 6 month time point in the Phase 3 clinical studies. See PTX-32, at 5. The FDA approved the NDA for Restasis in December 2002. Although the FDA stopped short of approving Restasis for treating the signs and symptoms of dry eye or KCS, it approved the drug for use to "increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation" associated with KCS. Id. at 1. Following the approval of its NDA, Allergan listed several patents in the Orange Book, including the Kaswan patent, the Ding I patent, and the six Restasis patents.

The four defendants have all filed ANDAs seeking permission from the FDA to manufacture and market generic versions of Restasis. Each of the ANDAs asserts that the ANDA applicant's generic product is bioequivalent to Restasis. Each of the defendants also filed a paragraph IV certification representing that the manufacture and sale of the applicant's product will not infringe any of the patents in suit and that the patents in suit are invalid on various grounds.

Allergan selected 13 claims from four of the Restasis patents to be litigated at trial. For purposes of simplifying the issues to be decided at trial, Allergan gave the defendants a covenant not to sue with respect to the claims in the two patents that are no longer asserted (the '162 patent and the '556 patent). See Dkt. No. 457, at 73-74; see also Dkt. No. 492, at 4; Dkt. No. 494, at 34 n.4. Allergan also agreed that the litigated claims in the remaining four patents would be representative of any other original asserted claims and that "any remedy that [the Court]

might enter as to the representative claims would apply equally to the unasserted claims." Dkt. No. 402, at 7-8.

The asserted claims are the following:

- From the '111 patent: claims 26 and 27 (both of which are dependent on claim 18);
- From the '048 patent: claim 1, claims 11, 13, and 14 (all of which are dependent on claim 1), and claim 23 (which is dependent on claim 22);
- From the '930 patent: claim 35 (which is dependent on claim 25);
- From the '191 patent: claim 13, claim 16 (which is dependent on claim 13), and claims 22, 26, and 27 (all of which are dependent on claim 21).

Those claims (and the independent claims from which they depend) are set out below:

- Claims 26 and 27 (and claim 18, from which both depend) of the '111 patent read as follows:

> **18.** A topical ophthalmic emulsion for treating an eye of a human, the topical ophthalmic 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,
> wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion.
>
> **26.** The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion is therapeutically effective in treating keratoconjunctivitis sicca.
>
> **27.** The topical ophthalmic emulsion of claim 18, wherein the topical ophthalmic emulsion is therapeutically effective in increasing tear production.

- Claims 1, 11, 13, 14, and 23 (and claim 22, from which claim 23 depends) of the ’048 patent read as follows:

> **1.** A method of increasing tear production in the eye of a human, 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 in increasing tear production.
>
> **11.** The method of claim 1, wherein the emulsion is administered to an eye of a human in an effective amount in increasing tear production, the blood of the human has substantially no detectable concentration of cyclosporin A.
>
> **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 0.5% by weight.
>
> **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.
>
> **22.** A method comprising:
> administering an emulsion topically to the eye of a human having keratoconjunctivitis sicca 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 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 increasing tear production in the human having keratoconjunctivitis sicca.

23. The method of claim 22, wherein the emulsion has a pH in the range of about 7.2 to about 7.6.

- Claim 35 of the ’930 patent (and claim 25, from which it depends) read as follows:

25. A topical ophthalmic emulsion for increasing tear production in an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic 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 therapeutically effective in increasing tear production in the eye of the human having keratoconjunctivitis sicca.

35. The topical ophthalmic emulsion of claim 25, wherein, when the topical ophthalmic emulsion is administered to an eye of a human in an effective amount in increasing tear production in the eye of the human having keratoconjunctivitis sicca, the blood of the human has substantially no detectable concentration of cyclosporin A.

- Claims 13, 16, 22, 26, and 27 of the ’191 patent (and claim 21, from which claims 22, 26, and 27 depend) read as follows:

16. The method of claim 13, wherein the method is effective in enhancing lacrimal gland tearing.

21. A method of restoring tearing, the method comprising topically administering to a human eye in need thereof a first topical ophthalmic emulsion at a frequency of twice a day, wherein the first topical ophthalmic 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;

wherein the method demonstrates a reduction in adverse events in the human, compared to administration of a second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day, the second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight; and

wherein the method achieves at least as much therapeutic efficacy as administration of the second topical ophthalmic emulsion to a human eye in need thereof at a frequency of twice a day.

22. The method of claim 21, wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

> **26**. The method of claim 21, wherein the method is effective in restoring lacrimal gland tearing.
>
> **27.** The method of claim 21, wherein the adverse events are selected from the group consisting of visual distortion and eye irritation and wherein the method results in a concentration of cyclosporin A in the blood of the human of less than about 0.1 ng/ml.

Following claim construction proceedings and extensive pretrial motions practice, the case was tried to the Court during the week of August 28, 2017. The issues that were contested at trial were the following: (1) whether the asserted claims of the Restasis patents would have been obvious in light of various combinations of prior art references, including the Ding I and Ding II patents and Sall; (2) whether the asserted claims of the Restasis patents were anticipated by the Ding I patent; (3) whether the asserted claims of the Restasis patents are invalid based on obviousness-type double patenting; (4) whether the Restasis patents are invalid because of nonjoinder of an inventor, Dr. Shulin Ding, who was a named inventor on the Ding I and Ding II patents; (5) whether the Restasis patents are invalid for lack of enablement because the limitation reciting "acrylate/C10-30 alkyl acrylate cross-polymer" ("the cross-polymer limitation") encompasses such a broad class of compounds that it would have required undue experimentation to determine which of them would be suitable for use in the claimed formulation; and (6) whether the formulation of Restasis has changed in a way such that the defendants' ANDAs do not infringe the Restasis patents under a narrow construction of the cross-polymer limitation.[10] The Court will enter findings of fact and conclusions of law with respect to each of those issues.

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[10] The polymer referred to in the cross-polymer limitation is sometimes referred to as a "co-polymer." For consistency, the Court will refer to it as a "cross-polymer" except when quoting record material.

DISCUSSION

I. Invalidity Based on Obviousness

Obviousness under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. Graham v. John Deere Co., 383 U.S. 1, 17 (1966). The underlying factual considerations "include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations" of nonobviousness, including commercial success of the patented product or method, a long-felt but unmet need for the functionality of the patented invention, and the failure of others who have unsuccessfully attempted to accomplish what the patentee has achieved. See Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 736 (Fed. Cir. 2013) (citing Graham, 383 U.S. at 17-18, and KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007)). The obviousness analysis should not be conducted "in a narrow, rigid manner," but should instead focus on whether a claimed invention is merely "the result[] of ordinary innovation," which is not entitled to patent protection. KSR Int'l, 550 U.S. at 427.

"A party seeking to invalidate a patent as obvious must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.'" Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc., 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting Procter & Gamble Co. v. Teva Pharms. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009)). Although the opposing party bears the burden of production as to secondary considerations of nonobviousness, the party seeking invalidation bears the ultimate burden of proving obviousness. Galderma, 737 F.3d at 738.

Based on the evidence at trial, as discussed in detail below, the Court finds (in part I.A.) that the formulation for Restasis falls within the range of values disclosed and claimed in the Ding I patent, and that the particular values for the components of Restasis did not produce unexpected results that would render the invention of Restasis non-obvious as of the priority date for the Restasis patents, September 15, 2003. The Court also finds (in part I.B.) that the objective indicia of nonobviousness do not overcome the strong showing of obviousness based on the Ding patents and the Sall paper. Finally, the Court finds (in part I.C.) that each of the other limitations in the 13 asserted claims of the Restasis patents is disclosed in Ding I or Sall, and that there was a clear motivation to combine the prior art, based on the close relationship between the Ding I patent, the Ding II patent, and the Sall reference, as well as a motivation to select the claimed formulation from the prior art range of component values.

A. Unexpected Results

The obviousness dispute in this case centers on Allergan's assertion that the Restasis formulation exhibited unexpected results compared to the prior art. Allergan recognizes that the Ding I patent discloses ranges of amounts of cyclosporin (0.05% to 0.40%) and castor oil (0.625% to 5.0%) that cover Restasis. Allergan argues, however, that the particular combination in Restasis of 0.05% cyclosporin and 1.25% castor oil is a critical value that produces unexpected results far better than would be expected for the range of values disclosed in Ding I. For that reason, Allergan contends that the critical value of 0.05% cyclosporin with 1.25% castor oil is patentable, even though it falls within the ranges disclosed and claimed in Ding I.

The defendants respond that the performance of the Restasis formulation is not surprising or unexpected compared to the performance of the prior art formulations disclosed in the Ding I patent. To begin with, the defendants argue that it would have been obvious to select the

Restasis formulation based on the information provided in Ding I. Beyond that, the defendants contend that even if the performance of the Restasis formulation would have been unexpected at the time the clinical studies were conducted, the results of those studies had been largely disclosed well before the 2003 priority date for the Restasis patents, and thus the performance of the Restasis formulation in those studies would not have come as a surprise to a person of skill in the art in 2003.[11]

The Federal Circuit has discussed what is necessary for patentability in cases such as this one: "[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, a relevant inquiry is whether there would have been a motivation to select the claimed composition from the prior art ranges." Allergan, Inc. v. Sandoz Inc., 796 F.3d 1293, 1304-05 (Fed. Cir. 2015); see also Galderma, 737 F.3d at 738. "In those circumstances, 'the burden of

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[11] The parties do not materially disagree about the level of skill of a person of ordinary skill in the art. Compare Dkt. No. 492, at 20 (according to defendants: "A skilled artisan in the relevant field as of September 15, 2003, would have some combination of: (a) experience formulating and/or treating patients with pharmaceutical products; (b) experience designing, preparing and/or selecting for treatment drug emulsions intended for topical ocular administration; and (c) the ability to understand the results and findings presented or published by others in the field.") with Dkt. No. 494, at 56 (according to Allergan: "[A] person of ordinary skill in the art is a person with a scientific degree, either Ph.D., M.D., M.S., or B.S., who has at least 2-3 years of experience developing pharmaceutical formulations or treatment methods for the eye, including emulsions, or is an ophthalmologist who has 2-3 years of experience treating dry eye or KCS, including with emulsions, who also has assisted in developing ophthalmic pharmaceutical formulations or in designing or running clinical trials on such formulations."); see also Dkt. No. 471, Trial Tr. 176 (description of person of skill by defendants' expert Dr. Hanes); Dkt. No. 473, Trial Tr. 30-31 (description of person of skill by defendants' expert Dr. Calman); Dkt. No. 474, Trial Tr. 79 (description of person of skill by Allergan's expert Dr. Loftsson); Dkt. No. 475, Trial Tr. 75 (Allergan's expert Dr. Perry: There is "no meaningful difference" between Dr. Calman's and Dr. Loftsson's definitions of a person of ordinary skill in the art.). Moreover, the parties' experts all testified that their opinions would be unchanged under either definition. See Dkt. No. 471, Trial Tr. 176-77 (Dr. Calman); Dkt. No. 473, Trial Tr. 31 (Dr. Hanes); Dkt. No. 474, Trial Tr. 80-81 (Dr. Loftsson); Dkt. No. 475, Trial Tr. 74-75 (Dr. Perry). The Court finds that Drs. Calman, Hanes, Loftsson, and Perry all qualify as persons of skill in the art in the context of the Restasis patents.

production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.'" Allergan, 796 F.3d at 1305 (quoting Galderma, 737 F.3d at 738); see also In re Peterson, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003) ("A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art," but "an applicant may overcome a *prima facie* case of obviousness by establishing 'that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.'"); In re Geisler, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) ("When an applicant seeks to overcome a prima facie case of obviousness by showing improved performance within a range that is within or overlaps with a range disclosed in the prior art, the applicant must 'show that the [claimed] range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.'" (quoting In re Woodruff, 919 F.2d 1575, 1578 (Fed. Cir. 1990))); In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating, in a case involving a composition claim including a compound with a molecular weight limited to a range within a larger range disclosed in the prior art, that "[o]ne way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected"). "The basic principle behind this rule is straightforward—that which would have been surprising to one of ordinary skill in a particular art would not have been obvious." In re Soni, 54 F.3d at 750.[12]

[12] In re Peterson, In re Geisler and In re Soni refer to the "prima facie case of

To be probative of nonobviousness, unexpected results must be "different in kind and not merely in degree from the results of the prior art." Galderma, 737 F.3d at 739 (quoting Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004)). "Results which differ by percentages are differences in degree rather than kind, where the modification of the percentage is within the capabilities of one skilled in the art at the time." Id. (citing In re Harris, 409 F.3d 1339, 1344 (Fed. Cir. 2005)); see also In re Huang, 100 F.3d 135, 139 (Fed. Cir. 1996); In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955).

Although the challenger bears the ultimate burden of proving obviousness by clear and convincing evidence, the patentee has the burden of production as to unexpected results. Galderma, 737 F.3d at 378. "Mere argument or conclusory statements in the specification" are not sufficient to establish unexpected results, which must be shown by factual evidence. In re Geisler, 116 F.3d at 1470; accord In re Soni, 54 F.3d at 750. The question whether an invention has produced unexpected results is an issue of fact. In re Harris, 409 F.3d at 1341.

Allergan argues that the validity of the asserted claims depends on whether the claimed formulation, which is Restasis, exhibited unexpected results as compared to the formulations disclosed in Ding I. See Dkt. No. 453, at 2 (Allergan's opening statement). More precisely, the validity of the claims turns on whether a person of skill in the art, being privy to all the pertinent

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obviousness" and the burden on the patentee to show unexpected results. Those cases dealt with overcoming obviousness rejections by the examiner during patent prosecution, not with district court actions in which an issued patent is entitled to a presumption of validity. In this district court case, as in Galderma, the ultimate burden of persuasion does not shift to the patentee but remains with the challenger throughout. See Galderma, 737 F.3d at 378; see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1079-80 (Fed. Cir. 2012).

prior art as of the September 2003 priority date of the Restasis patents, would have found the performance of the Restasis formulation in the Phase 3 clinical studies to be unexpected.

As noted, during the prosecution of the '857 application Allergan "concede[d] [to the PTO] that it would have been obvious to modify examples 1A-1E of the Ding reference to arrive at Composition II [the Restasis formulation] of the present application." DTX-1291A, at 481. Allergan explained that the differences between Examples 1A-1E of the Ding I patent and the Restasis formulation "are insignificant"; that one of ordinary skill in the art "would readily envisage" the Restasis formulation; and that "there would have been a reasonable expectation of success" with the Restasis formulation. Id. Also included was a table illustrating how Restasis would be "readily envisage[d]" based on Examples 1B, 1D, and 1E of the Ding I patent:

Compositions of the Ding reference compared to Composition II of the present application

	Ding *et al.* Example 1B	Ding *et al.* Example 1D	Ding *et al.* Example 1E	Composition II
Cyclosporin A	0.20 %	0.10 %	**0.05 %**	**0.05 %**
Castor Oil	5.00 %	**1.250 %**	0.625 %	**1.250 %**
Polysorbate 80	1.00 %	1.00 %	1.00 %	1.00 %
Pemulin®	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
cyclosporin : castor oil	**0.04**	0.08	0.08	**0.04**

Id. at 480.

More than four years later, while prosecuting what became the Restasis patents, Allergan withdrew its concession and argued that the applications claiming the Restasis formulation were patentable over the Ding I patent because they showed unexpected results for the Restasis formulation as compared to the ranges claimed in Ding I and the particular examples disclosed in the specification of Ding I. As evidentiary support for that position, Allergan submitted Dr. Schiffman's declaration to the examiner. In that declaration, PTX-2A, Dr. Schiffman stated that the Restasis formulation was "equally or more therapeutically effective" than the 0.1% cyclosporin/1.25% castor oil formulation set forth in Example 1D of Ding I, and that "[t]his result was surprising and completely unexpected." PTX-2A at 555 (emphasis in original); see also Dkt. No. 469, Trial Tr. 88. After reviewing Dr. Schiffman's declaration, the PTO issued the patents in suit. See, e.g., PTX-2C (notice of allowability for the '111 patent); Dkt. No. 469, Trial Tr. 90. Dr. Schiffman agreed that it would be fair to say that his declaration was instrumental in persuading the Patent Office to grant the applications. Dkt. No. 469, Trial Tr. 90.

The core inquiry on the issue of obviousness is whether the results obtained for the Restasis formulation would have been surprising to a person of skill in the art in light of what was known in the prior art as of September 15, 2003. As discussed in detail in the sections below, the Court finds (in part I.A.1.) that the 0.05% cyclosporin/1.25% castor oil formulation did not perform significantly better than other formulations known in 2003. The Court further finds (in parts I.A.2. and I.A.3.) that neither Dr. Schiffman's declaration to the PTO nor the FDA's Medical Review of the Restasis NDA provides persuasive evidence to the contrary. Finally, the Court finds (in part I.A.4.) that even if there was initial surprise regarding the performance of the Restasis formulation in the Phase 3 studies in 1999, intervening disclosures

in the art would have rendered that result unsurprising to a person of skill in the art by the 2003 priority date for the Restasis patents.

1. Restasis did not outperform known formulations

Allergan contends that the results of the Phase 2 and Phase 3 studies show surprising efficacy for the Restasis formulation as compared to Examples 1D and 1E in Ding I. According to Allergan, the 0.1% cyclosporin/1.25% castor oil emulsion (Example 1D in Ding I) outperformed the 0.05% cyclosporin/0.625% castor oil emulsion (Example 1E in Ding I) in the Phase 2 trial. Allergan further asserts that in the Phase 3 trials it was surprising to discover that the 0.05% cyclosporin/1.25% castor oil emulsion (Restasis) outperformed the 0.1% cyclosporin/1.25% castor oil emulsion. The Court concludes that the evidence at trial does not support either of Allergan's conclusions about what was shown by the Phase 2 and Phase 3 study results.

a. Phase 2: the 0.05% cyclosporin/0.625% castor oil formulation performed similarly to 0.1% cyclosporin/1.25% castor oil formulation

Allergan contends that the Stevenson paper, which published the results from the Phase 2 study, shows that the 0.1% cyclosporin formulation outperformed the 0.05% cyclosporin formulation. For support, Allergan points to Stevenson's Figure 1 (depicting the change from baseline in temporal rose bengal staining), Figure 2 (depicting the change from baseline with respect to superficial punctate keratitis or "SPK"), and Figure 5 (depicting the change from baseline in ocular surface disease index ("OSDI")). For those efficacy measures, the bar graphs in the figures show greater improvement for the 0.1% cyclosporin/1.25% castor oil formulation than for the 0.05% cyclosporin/0.625% castor oil formulation.

Allergan, however, ignores Stevenson's Figure 3 (depicting the change from baseline with respect to sandy or gritty feeling) and Figure 4 (depicting the change from baseline with respect to ocular dryness), both of which show that the 0.05% cyclosporin/0.625% castor oil formulation did better than the 0.1% cyclosporin/1.25% castor oil formulation. The Stevenson paper concludes that the 0.1% cyclosporin formulation provided the most consistent improvement in objective and subjective endpoints, while the 0.05% formulation produced the most consistent improvements in patient symptoms. DTX-1018, at 971, 973-74. In sum, according to Stevenson, both the 0.05% and 0.1% cyclosporin formulations did well on different efficacy measures, from which Stevenson concluded that both formulations warranted further study. Id. at 967, 974 ("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.").

Stevenson also reported that "[t]here was no clear dose-response relationship" shown in the Phase 2 study between the tested cyclosporin formulations, i.e., the increase in cyclosporin did not result in an increase in clinical efficacy. DTX-1018, at 967; see also id. at 973. In a typical dose-response relationship, an increase in the dose of the active ingredient results in an increase in the therapeutic effect of the drug. Dkt. No. 474, Trial Tr. 141. Therapeutic efficacy may continue to increase until it reaches a plateau, at which point further increases in the amount of the active ingredient no longer result in an increase in therapeutic effect. See Dkt. No. 473, Trial Tr. 66; Dkt. No. 474, Trial Tr. 141-42. If there is no dose-response relationship between lower and higher amounts of a drug (such as after the efficacy plateau is reached), then there is no reason to use greater amounts of the drug in an effort to achieve greater therapeutic efficacy. Thus, there would be no motivation to move from a 0.05% cyclosporin formulation to a 0.1%

cyclosporin formulation if the higher concentration provided no greater therapeutic effect. Dkt. No. 473, Trial Tr. 66, 148-49; Dkt. No. 474, Trial Tr. 141-42. Because Stevenson noted the lack of a dose-response relationship between the tested formulations, a person of ordinary skill would not understand Stevenson's paper to suggest using the 0.1% cyclosporin formulation over the 0.05% cyclosporin formulation. See Dkt. No. 473, Trial Tr. 66.

Allergan argues that, contrary to what was reported in the Stevenson paper, the Phase 2 study showed a dose-response effect between the 0.05% and 0.1% cyclosporin formulations. Allergan's clinical expert, Dr. Henry Perry, testified that he interpreted the data in Stevenson to show that there was a dose-response effect between the 0.05% and 0.1% cyclosporin concentrations, and that the dose-response effect disappeared only at higher cyclosporin concentrations, such as in the 0.2% and 0.4% cyclosporin formulations tested in Stevenson. See Dkt. No. 474, Trial Tr. 142-44; Dkt. No. 475, Trial Tr. 90-92.

The Court does not credit Dr. Perry's testimony on that point. It is contrary to Stevenson, which is a paper sponsored by Allergan and co-authored by Dr. Brenda Reis, the Allergan team leader on the cyclosporin project. Stevenson stated, three times, that there was no clear dose-response effect among any of the tested cyclosporin formulations. DTX-1018, at 967, 973, 974. In addition, Allergan's present position as to the dose response is based on two measurements—temporal rose bengal staining and superficial punctate keratitis—on which the 0.1% cyclosporin formulation performed better than the 0.05% cyclosporin formulation. But Allergan's analysis ignores the measurements on which the 0.05% formulation outperformed the 0.1% formulation. Stevenson reported that, among the four tested concentrations, the 0.05% and 0.1% formulations did best on different efficacy measures, not that 0.1% did better than 0.05% globally. Id. at 967, 973-74.

Previous statements by Allergan also contradict its present contention (and Dr. Perry's testimony) that the Phase 2 study showed a dose-response effect between the 0.05% and 0.1% cyclosporin formulations. In a contemporaneous 1999 report on the Phase 3 trials, submitted as part of the Restasis NDA, Allergan stated that the Phase 3 results "did not indicate a clear dose-response for cyclosporine." DTX-1219, at 96. The lack of any dose-response effect between the 0.05% and 0.1% formulations in the Phase 3 trials was "not surprising," the report stated, "because the results of the Phase 2 study suggested that the 0.05% and 0.1% cyclosporin are on the plateau of the therapeutic response curve." Id.; accord Dkt. No. 470, Trial Tr. 110-11. When that report was written in 1999, Allergan had interpreted both the Phase 2 and Phase 3 data as showing no dose response between the 0.05% and 0.1% cyclosporin formulations tested in those sets of studies. In addition, the Sall paper, which analyzed the Phase 3 studies and was sponsored by Allergan, reached the same conclusion as the Stevenson paper and Allergan's 1999 report, stating that "[t]here was no dose-response effect" between the 0.05% and 0.1% cyclosporin formulations. DTX-1017A, at 631.[13]

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[13] In an effort to support its theory that there was a dose response between the 0.05% and 0.1% cyclosporin formulations, Allergan points to a passage in the Ding I patent that discusses an experiment in which Examples 1A through 1D were "tested for ocular bioavailability in rabbits; and the therapeutic level of cyclosporin was found in the tissues of interest after dosage." Ding I patent, col. 5, ll. 18-22. At trial, Dr. Perry testified that the omission of Example 1E (the 0.05% cyclosporin formulation) from that experiment suggests that the Ding I inventors believed that the 0.05% cyclosporin formulation had no appreciable therapeutic effect. Dkt. No. 475, Trial Tr. 84 (stating that the failure to test Example 1E suggests that the inventors of Ding I "thought that the other levels were more promising and that the lowest level [0.05% cyclosporin] was too low"). The Court rejects that inference from the failure to test Example 1E, for two reasons. First, the Court credits the testimony of the defendants' clinical expert, Dr. Andrew Calman, (a) that there are many possible reasons that Ding I did not mention Example 1E, and (b) that a person of skill would reasonably infer that the 0.05% cyclosporin formulation would demonstrate at least some efficacy because 0.05% is included in the claimed range in the Ding I patent. Dkt. No. 473, Trial Tr. 100-01. Second, during the prosecution of the earlier abandoned

Beyond noting the absence of a dose-response effect between the 0.05% and 0.1% cyclosporin formulations, the Sall paper summarized the results of the Phase 2 clinical trial as "demonstrat[ing] that such CsA treatment was safe and resulted in significant improvements in the signs and symptoms of the disease." DTX-1017A, at 631, 632. Sall explained that "[t]he objective of the [Phase 3] studies described here was to compare the efficacy and safety of twice daily [cyclosporin A], 0.05% and 0.1%, ophthalmic emulsions to vehicle in the treatment of moderate to severe dry eye disease." Id.

Thus, the Phase 2 study revealed that the emulsion formulations all generally worked and were safe. See DTX-1018, at 967 (Stevenson concluded that all "[c]yclosporin 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."). It was the Phase 3 studies, not the Phase 2 study, that were intended to determine whether the approved drug should contain a 0.05% cyclosporin emulsion or a 0.1% cyclosporin emulsion. Allergan's flawed effort to convert the Phase 2 study into an assessment of the relative efficacy of the 0.05% and 0.1% cyclosporin formulations lies at the heart of the problem with its "unexpected results" analysis.

The Phase 2 study was small and was not designed to reveal statistically significant differences between the various tested formulations. Stevenson stated that "[b]ecause this [Phase 2 study] was the first clinical trial conducted with this new cyclosporin formulation, it was

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'857 application to which the asserted patents claim priority, Allergan disclaimed precisely the same negative inference argument that was made by Dr. Perry at trial. DTX-1291A, at 481-82 (Allergan "concede[d]" that the Ding I patent does not indicate that Example 1E lacks therapeutic efficacy based on the absence of testing, as that argument "was based on an unfounded negative implication" and on "logic [that] elevates speculation above evidence, and permits one to draw any conclusion, no matter how incredible.").

designed to function as a pilot study for future investigations." DTX-1018, at 969. At trial, Dr. Schiffman explained that "Phase [2] is when you do begin to have an interest in evaluating safety and efficacy. Typically it is dose ranging. You use multiple doses to begin to see that you're getting some sort of treatment effect." Dkt. No. 469, Trial Tr. 32; see also DTX-1018, at 967 (the title of the Stevenson paper was "A Dose-Ranging, Randomized Trial"). The defendants' expert, Dr. Andrew Calman, agreed: "[J]ust to put [the Phase 2 study] in context, this is a dose ranging study with smaller treatment groups. So as I said, you can find some parameter where one's better and some parameter where the other is better, but that's why you do statistic[s]." Dkt. No. 473, at 126.

The small size of the Phase 2 study makes it difficult to draw reliable conclusions about the relative efficacy of different formulations. From the approximately 160 patients who were initially enrolled in the Phase 2 study, Allergan identified a subpopulation for that study represented by approximately 90 patients with particular characteristics of interest (moderate-to-severe dry eye), of which 88 completed the study. Allergan decided to target that population group for further investigation of its cyclosporin emulsions in the Phase 3 studies. See DTX-1018, at 969-70 & tbl. 1; Dkt. No. 476, Trial Tr. 44-45. It is the smaller subgroup of 88 patients in the Phase 2 study that provided the relevant data upon which Allergan bases its argument of unexpected results.

Those 88 patients were divided into five groups—four of the groups were given different concentrations of the cyclosporin formulation, and one group was given just the castor-oil-only vehicle. Thus, the comparisons between the patients given the 0.05% cyclosporin formulation and those given the 0.1% cyclosporin formulation were done on two very small groups of only 17 and 18 patients, respectively. DTX-1018, at 970, tbl.1.

The defendants' statistics expert, Dr. Daniel Bloch, examined the results of the small Phase 2 study. He looked in particular at the Schirmer tear test scores and corneal staining data. According to Dr. Schiffman's declaration, which Allergan submitted to the PTO to show the "unexpected results" achieved in the testing of the Restasis formulation, those were the endpoints of interest in Phase 2. See PTX-2A, at 553-67 (¶ 7 & Ex. B). Given the small size of the study and the even smaller size of the subgroup of interest, Dr. Bloch determined that there were no statistically significant differences in efficacy between the 0.05% and 0.1% cyclosporin formulations at the end of the treatment period in Phase 2 for either the Schirmer scores or the corneal staining data. See Dkt. No. 476, Trial Tr. 51-53.

As explained by Dr. Bloch, a pair-wise (i.e., head-to-head) comparison between the mean values of two groups of data can be used to derive a p-value, which indicates whether any differences in the two groups of data are statistically significant, rather than simply being the product of random chance. For example, one could compare (a) the mean improvement in Schirmer scores over a three-month period for patients treated with the 0.05% cyclosporin formulation to (b) the mean improvement in Schirmer scores over a three-month period for patients treated with the 0.1% cyclosporin formulation. A pair-wise comparison of those two means could be used to derive a p-value indicating whether there was a real difference between the average improvement in Schirmer scores for the 0.05% cyclosporin formulation and the average improvement in Schirmer scores for the 0.1% cyclosporin formulation. A small p-value, such as $p = 0.05$, would indicate that the observed difference between those averages is meaningful, in that the difference is the result of random chance only 5% of the time. A large p-value, such as $p = 0.30$, would mean that the observed difference is the result of random chance 30% of the time.

In designing clinical trials for drugs, persons of skill often look for a 95% confidence level, which corresponds to a p-value less than or equal to 0.05, before drawing conclusions about data-based comparisons. In statistical parlance, a p-value less than or equal to 0.05 is regarded as "statistically significant." See, e.g., DTX-1018, at 969 ("A two-sided test with P = 0.05 was considered statistically significant for all main effects."); DTX-1017A, at 634 ("Specifically, a pair wise comparison between either cyclosporine group and vehicle group[] is considered statistically significant if and only if, [among other things,] . . . the pair wise comparison between cyclosporine and vehicle is significant at the 0.05 level.").

Dr. Bloch pointed to the portion of Allergan's NDA submission that contains pair-wise comparisons of the 0.05% and 0.1% cyclosporin formulations in Phase 2 for Schirmer scores and corneal staining at week 12 (the end of the treatment period). The pair-wise comparison of those two formulations for Schirmer tear test scores at week 12 corresponded to an extremely high p-value of 0.834, i.e., it was not remotely close to showing a statistically significant difference between the two. Dkt. No. 476, Trial Tr. 52; PTX-16D, at AGN_RES0012942 (Table 14a).[14]

[14] The parties have not clarified whether Allergan performed pair-wise comparisons of categorized Schirmer scores, as distinguished from raw Schirmer scores, for those two formulations in Phase 2. Although Allergan's NDA contains separate tables for each endpoint, the table of pair-wise comparisons for the raw Schirmer scores appears to be an exact copy of the table for the categorized Schirmer scores. Compare PTX-16D, at AGN_RES0012942 (Table 14a: Schirmer Tear Values Pairwise Comparisons) with id. at AGN_RES0012945 (Table 16a: Categorized Schirmer Tear Values Pairwise Comparisons); see also id. at AGN_RES0012941 (reporting p-values and among-group p-values for Schirmer tear values); id. at AGN_RES0012944 (reporting same p-values and among-group p-values for categorized Schirmer tear values even though the data is different). As it appears that the parties, as well as Stevenson, treated the pair-wise comparisons as calculated based on the raw Schirmer data, not the categorized Schirmer data, see Dkt. No. 469, Trial Tr. 73-74; Dkt. No. 476, Trial Tr. 114-15; DTX-1018, at 971, the Court will assume the same. But the Court notes that the analysis of unexpected results would not change if those pair-wise comparisons were in fact calculated based on the categorized Schirmer data.

The pair-wise comparison of those two formulations for corneal staining data at week 12 revealed a p-value of 0.112, a lower value, but still more than two times higher than would permit a finding of statistical significance. Dkt. No. 476, Trial Tr. 51 (citing DTX-1191, at 248).[15]

According to Allergan, the Court should not ignore study results simply because the p-value was above 0.05. The Court agrees, up to a point. If a person of skill assigns meaning to results when the p-value is 0.0499, the Court sees no reason why that person of skill would suddenly assign no meaning to those same results if the p-value were 0.0501. With such close p-values, the odds that the observed results are the product of random chance are essentially the same. Thus, in considering what a person of skill would expect, the Court will not draw a rigid, artificial line at a p-value of 0.05: Results accompanied by a p-value of slightly more than 0.05 would also be likely to inform the reasonable expectations of one of skill in the art.[16]

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[15] The p-values for pair-wise comparisons of the two formulations' categorized Schirmer tear test scores without anesthesia at weeks 4 and 8 were both very high—0.651 (week 4) and 0.790 (week 8). PTX-16D, at AGN_RES0012945 (Table 16a). For corneal staining, there was a statistically significant difference at week 8 (p-value of 0.049), but none at week 4 (p-value of 0.217). DTX-1191, at 248.

[16] Allergan notes that Dr. Bloch, an expert in biostatistics, is not "a person of skill in the art" for purposes of this case. While that may be true, a person of skill in the art would be familiar with clinical trials and would understand and look to statistics to interpret clinical data. See Dkt. No. 492, at 20 (according to defendants: "A skilled artisan in the relevant field as of September 15, 2003, would have . . . the ability to understand the results and findings presented or published by others in the field."); Dkt. No. 494, at 56 (according to Allergan: "[A] person of ordinary skill in the art is a person . . . who also has assisted in developing ophthalmic pharmaceutical formulations or in designing or running clinical trials on such formulations."). Allergan (in Stevenson, Sall, and its NDA) as well as the FDA interpreted the results of Allergan's clinical trials by looking at statistical analyses and applying the concept of statistical significance. Dr. Bloch's testimony is therefore relevant to the interpretation of the results of Allergan's clinical trials.

Nonetheless, the Court rejects Allergan's contention that a person of skill would look at the Schirmer scores and corneal staining results in Phase 2 and conclude that the 0.1% cyclosporin formulation was more effective than the 0.05% cyclosporin formulation. For one thing, Allergan has not explained why those two endpoints, in particular, are important in determining effectiveness. Even if Schirmer scores and corneal staining were shown to be the two most relevant endpoints, the p-values of 0.834 and 0.112 reveal that the difference observed between the 0.1% and 0.05% formulations for the Schirmer scores may be the result of random chance more than 83% of the time, and on corneal staining, the result of random chance more than 11% of the time. Even for corneal staining, the p-value is more than twice as large as the value that clinicians usually regard as representing a real difference between two means.

Nor does Allergan find support in the rest of the data for its position that the 0.1% formulation outperformed the 0.05% formulation in the Phase 2 study. The defendants' expert Dr. Calman reviewed the Phase 2 data in Stevenson, which reported results on 14 efficacy measures: rose bengal staining (temporal), rose bengal staining (nasal),[17] corneal staining (allowing the detection of SPK), Schirmer scores without anesthesia, tear film debris, tear break-up time, artificial tear use, OSDI score, stinging or burning, itching, sandy or gritty feeling,

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[17] "Rose bengal staining (temporal)" refers to the rose bengal staining test results for the part of the conjunctiva that is on the outer side of the eye, i.e., on the side closer to the temple. "Rose bengal staining (nasal)" refers to the rose bengal staining test results for the part of the conjunctiva that is on the inner side of the eye, i.e., on the side closer to the nose. Dkt. No. 473, Trial Tr. 75.

dryness, light sensitivity, and pain. He looked at those results at all measured time points: week 4, week 8, week 12, post-treatment week 2, and post-treatment week 4.[18]

Based on his analysis, Dr. Calman determined that the differences between the 0.05% and 0.1% formulations were statistically significant for only 2 of the 58 measured categories. First, he determined that there was a statistically significant difference favoring the 0.1% formulation over the 0.05% formulation in the OSDI score, but only at week 12. Second, he determined that there was a statistically significant difference favoring the 0.1% formulation over the 0.05% formulation in the temporal rose bengal conjunctival staining, but only at post-treatment week 2. See Dkt. No. 473, Trial Tr. 72. The Court does not find that those two individual points of statistical significance, out of all of the tested categories and time points, are sufficient to demonstrate a real difference in effectiveness between the 0.05% and 0.1% cyclosporin formulations. Significantly, during the prosecution of the Restasis patents, Allergan did not rely on either of those two categories as proof of unexpected results.[19]

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[18] Dr. Calman noted that his summary did not account for a few missing data points, because Stevenson did not report results (i) for tear film debris at week 4 and post-treatment weeks 2 and 4, (ii) for tear break-up time at weeks 4 and 8 and post-treatment weeks 2 and 4, (iii) for artificial tear use at weeks 4 and 8, and (iv) for OSDI at weeks 4 and 8 and post-treatment week 2. For some of those results missing from Stevenson, such as OSDI at weeks 4 and 8 and post-treatment week 2, it appears that Allergan did not collect that data in Phase 2. See PTX-16D, at AGN_RES0013005. In any event, Allergan did not rebut Dr. Calman's summary of the Phase 2 results.

[19] Before the PTO, as well as during trial before this Court, Allergan relied heavily on the Schirmer scores and corneal staining data but did not make much of the subjective OSDI measurement in the Phase 2 study. In its proposed Findings of Fact and Conclusions of Law, however, Allergan claims that OSDI is entitled to more weight "'because it covers a much broader understanding of what th[e] patient is feeling' and actually overlaps many of the subjective symptoms such as gritty feeling and ocular dryness." Dkt. No. 494, at 20 (quoting Dr. Perry's testimony at Dkt. No. 475, Trial Tr. 94); see also id. at 10. That single point of statistical significance, at one time point, does not demonstrate the superiority of the 0.1% cyclosporin

Allergan highlights various data points to show how well the 0.1% formulation performed relative to baseline in the Phase 2 study. Those observations, however, are not directly pertinent to the question whether the 0.1% formulation did better than the 0.05% formulation. And the evidence shows that it did not. For example, for the change on temporal rose bengal staining scores, the 0.1% formulation demonstrated a statistically significant improvement over baseline, whereas the same could not necessarily be said of a comparison of other formulations to baseline. See DTX-1018, at 970 & Fig. 1. But on a second set of endpoints, including ocular dryness and sandy or gritty feeling, the 0.05% formulation performed significantly better than baseline at most time points, while the 0.1% formulation did not. See id. at 971 & Figs. 3 and 4.

On a third set of efficacy measures, including corneal staining, all tested formulations, including the castor-oil-only vehicle, showed an improvement over baseline. For example, the improvement in corneal staining was statistically significant for all formulations at all time points, except for the 0.05% formulation at week 12 and post-treatment week 4. See PTX-16D, at AGN_RES0012947; accord DTX-1018, at 971 & Fig. 2. And on a fourth set of efficacy measures, including Schirmer tear test scores, neither the 0.1% nor the 0.05% cyclosporin formulations showed a statistically significant improvement over baseline. See PTX-16D, at AGN_RES0012941 (only the 0.4% cyclosporin formulation demonstrated statistically significant improvements over baseline—at week 4 and post-treatment week 4). The 0.1% formulation, however, approached statistical significance as compared to baseline for Schirmer tear test scores

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formulation as compared to the 0.05% cyclosporin formulation, particularly in light of the other subjective measurements favoring the 0.05% formulation in Phase 2, see DTX-1018, at Figs. 3-4, and in light of Stevenson's conclusion that "cyclosporin A 0.05% gave the most consistent improvement in patient symptoms," id. at 967.

at weeks 8 and 12 (p-values of 0.051 and 0.055). Id.; accord DTX-1018, at 970-71. And the 0.05% formulation, as compared to baseline for Schirmer tear test scores, had a relatively low p-value at week 8. See PTX-16D, at AGN_RES0012941 (p-value of 0.086). Notably, for corneal staining and Schirmer tear test scores, the tests that Allergan principally relied on for its claim of unexpected results, either both the 0.1% and 0.05% cyclosporin formulations demonstrated statistically significant improvements over baseline, or neither did.

Importantly, the results highlighted by Allergan are measured against the baseline; those results say nothing about whether the 0.1% formulation showed a statistically significant improvement as compared to the 0.05% cyclosporin formulation. See, e.g., PTX-16D, at AGN_RES0012942 (for Schirmer tear test values at weeks 8 and 12, the pair-wise comparisons of the 0.05% and 0.1% cyclosporin formulations revealed extremely high p-values of 0.790 and 0.834). As previously noted in connection with Dr. Calman's testimony, the observed difference between the 0.1% and 0.05% cyclosporin formulations was statistically significant for only 2 of 58 data points.

The table below summarizes the meaningful differences of more than a dozen outcomes measured at the end of the treatment period (week 12) in the Phase 2 study for the preferred target subpopulation. Allergan points to some of the data in the first five columns showing, for example, that the 0.1% formulation demonstrated a statistically significant improvement over baseline in corneal staining, or that the 0.1% formulation demonstrated a statistically significant improvement as compared to the vehicle in temporal rose bengal conjunctival staining. But the relevant comparisons are those between the 0.05% and 0.1% formulations, which appear in the last column. The only statistically significant difference in that key category appears in one endpoint, the OSDI score, a subjective measurement upon which Allergan did not rely to support

its claim of unexpected results before the PTO. And for all 14 endpoints at the end of the treatment period, the p-value was less than 0.10 for only 2 of the 14—OSDI and blurred vision—both of which favored the 0.1% cyclosporin formulation.[20] So even considering p-values up to twice the usual standard of 0.05, there was no substantial difference in performance between the two cyclosporin formulations.

Efficacy Measure	**Vehicle versus Baseline**	**0.05% versus Baseline**	**0.1% versus Baseline**	**0.05% versus Vehicle**	**0.1% versus Vehicle**	**0.05% versus 0.1%**
Schirmer (without anesthesia)	No (p = 0.234)	No (p = 0.156)	No (p = 0.055)	No (p = 0.804)	No (p = 0.640)	No (p = 0.834)
Corneal Staining (SPK)	Yes (p = 0.041)	No (p = 0.131)	Yes (p < 0.001)	No (p = 0.460)	No (p = 0.327)	No (p = 0.112)
Tear Film Debris	No (p = 0.129)	No (p = 0.063)	Yes (p = 0.031)	No (p = 0.757)	No (p = 0.534)	No (p = 0.714)
Rose Bengal Conjunctival Staining (Nasal)	Yes (p = 0.025)	Yes (p < 0.01)	Yes (p < 0.01)	No (p = 0.245)	No (p = 0.203)	No (p = 0.649)
Rose Bengal Conjunctival Staining (Temporal)	Yes (p = 0.047)	No (p = 0.398)	Yes (p < 0.001)	No (p = 0.901)	Yes (p = 0.046)	No (p = 0.113)
Dryness	No	No	No	No	No	No

[20] Although this table was created by the Court, the entries in the table were collected or derived from the following evidence admitted at trial: PTX-16D, at AGN_RES0012941-42, AGN_RES0012947, AGN_RES0012949, AGN_RES0012952-55, AGN_RES0012984, AGN_RES0012994-13001, AGN_RES0013005-06, AGN_RES0013012; and DTX-1191, at 248, 250, 267, 275-78. P-values less than or equal to 0.05 ("statistically significant") are shaded gray.

	(p = 0.438)	(p = 0.125)	(p = 0.250)	(p = 0.550)	(p = 0.866)	(p = 0.654)
Sandy / Gritty Feeling	No (p = 0.125)	Yes (p = 0.004)	No (p = 0.113)	Yes (p < 0.001)	Yes (p = 0.018)	No (p = 0.225)
Burning / Stinging	No (p > 0.999)	No (p > 0.999)	No (p = 0.344)	No (p = 0.892)	No (p = 0.442)	No (p = 0.589)
Pain	No (p = 0.973)	No (p = 0.688)	No (p = 0.375)	No (p = 0.479)	No (p = 0.301)	No (p = 0.717)
Itching	No (p = 0.422)	No (p = 0.125)	No (p = 0.117)	No (p = 0.079)	No (p = 0.066)	No (p = 0.932)
Sensitivity to Light	No (p = 0.183)	No (p = 0.250)	No (p = 0.781)	Yes (p = 0.041)	No (p = 0.427)	No (p = 0.212)
Blurred Vision	No (p > 0.999)	No (p > 0.999)	Yes (p = 0.031)	No (p = 0.508)	No (p = 0.216)	No (p = 0.065)
OSDI	No (p = 0.673)	No (p = 0.480)	Yes (p = 0.004)	No (p = 0.879)	No (p = 0.095)	Yes (p = 0.049)
Artificial Tear Use	--	--	--	No (p = 0.325)	No (p = 0.097)	No (p = 0.133)

Based on the Phase 2 results, the Court finds that a person of skill in the art would not consider the 0.1% cyclosporin/1.25% castor oil formulation to be more effective than the 0.05%

cyclosporin/0.625% castor oil formulation in practice. For similar reasons, the Court finds that the publication of the Phase 2 results in Stevenson did not teach away from a formulation containing 0.05% cyclosporin.

Allergan argues that even if statistical significance is lacking, the Court should consider clinical significance in assessing whether the 0.1% cyclosporin formulation out-performed the 0.05% cyclosporin formulation in the Phase 2 study. An event or set of results may be clinically significant, Allergan argues, even if that event or set of results is not statistically significant. For instance, to cite an example used at trial, there may be a serious adverse event, such as death, in one or two patients in a large study. Although the deaths may not be statistically significant, they may be clinically significant, in that clinicians would pay close attention to those results in deciding whether to administer a drug. See Dkt. No. 476, Trial Tr. 33-34. Conversely, a particular result may be statistically significant but clinically irrelevant. For example, a change in the amount of cyclosporin in the formulation may result in a statistically significant increase (with a very low p-value) in the concentration of cyclosporin the bloodstream, but the increased amount may be so small, given the known toxicity level for the drug, that the increase is of no clinical concern. E.g., Dkt. No. 475, Trial Tr. 107.

While the difference between clinical significance and statistical significance can be useful for some purposes, Allergan has failed to explain why clinical significance, without statistical significance or something close to it, is relevant to the issue of unexpected results. Even if clinicians would pay attention to some events that are important but not statistically significant, that does not mean that clinicians would expect those events to happen. As in the previous example, a clinician would be likely to be concerned about the possibility of death from a particular drug even if the reported deaths were few and were likely the product of random

chance (i.e., had an extremely high p-value such as 0.90). But whatever choice the clinician might make in practice, and whatever the reason for that choice, the clinician's expectation would be that the patient would not die as a result of taking the drug, given the large p-value. See Dkt. No. 473, Trial Tr. 123-24.

Thus, a clinician might be concerned about bare results, even when they have not been subjected to statistical analysis, and may take action based on those bare results in the absence of the availability of more concrete confirmation that those results are meaningful. But subjective impressions created by bare results are not the appropriate measure by which to compare the efficacy of two different doses of an active ingredient in a testing environment. And any unexpected results must be supported by factual, not speculative, evidence. See In re Geisler, 116 F.3d at 1470; In re Soni, 54 F.3d at 750; see also, e.g., In re Inland Steel Co., 265 F.3d 1354, 1365-66 (Fed. Cir. 2001) (affirming Board's determination of no unexpected results in light of, among other things, the "insufficient data" where the patentee "offered only a few data points from one experiment" and "did not offer comprehensive test results").

As Dr. Calman explained, "[i]n order to really determine whether the claimed 0.05 percent emulsion is better than any other emulsion," clinicians "do these . . . types of clinical trials." Dkt. No. 473, Trial Tr. 122-23. When "we're talking about efficacy, we're talking about clinical trials in this setting, and we compare things not just by eyeballing raw numbers but by doing statistical analysis, as Allergan did" in its NDA. Id. at 123. "[I]f you want to compare a particular emulsion against another particular emulsion, you need to do a head-to-head study, and you need to do a statistical analysis." Id. Based on the statistical analyses of Allergan's Phase 2 and Phase 3 studies, Dr. Calman concluded that the 0.05% and 0.1% cyclosporin formulations in Phase 2 performed equivalently: "There was no statistically significant

difference between them. And as a clinician, they are materially not different." Dkt. No. 473, Trial Tr. 146.

By contrast, Allergan's witness Dr. Schiffman testified that, based on Stevenson, he understood that the 0.1% cyclosporin formulation did better than the 0.05% cyclosporin formulation in Phase 2, and he formed an expectation that the same would occur in Phase 3. Dkt. No. 469, Trial Tr. 122-23. He was therefore "surprised that [0].05 performed better" in Phase 3. Dkt. No. 469, Trial Tr. 124. According to Dr. Schiffman, "we're trying to make too much out of statistical techniques when the bigger picture is – is – is really sufficient, I think. [0].05 performed better in Phase 3. That, to me, is not really so much up to debate." Id.; see also id. at 123 (Dr. Schiffman: "That there are no p-values for me then and now mean nothing.").

Although the Court will not draw a rigid line at the p-value of 0.05, the Court rejects Dr. Schiffman's suggestion that statistical techniques can be disregarded in favor of looking at the "bigger picture" of superior performance. As Dr. Calman explained:

> Statistics are the way that we, as clinicians and scien[tists,] communicate with regard to these types of data and to determining whether drugs work. The FDA determine – requires statistical analysis to determine if drugs work in general. And when you submit a paper to a peer-reviewed journal, they want to see a statistical analysis. And all of this is just to be sure that any apparent differences are real and not just the result of random noise.

Dkt. No. 473, Trial Tr. 123-24; see also Dkt. No. 476, Trial Tr. 43-44 (Dr. Bloch: Without statistical significance in the clinical trial setting, "one doesn't have the confidence that" there really is an effect; "the difference . . . may be just a chance random finding."); see also DTX-1017A, at 638 (Sall: "The data presented here demonstrate [statistically significant] improvements [of the 0.05% and 0.1% cyclosporin formulations over vehicle] in objective and

subjective measures of dry eye disease that are beyond what can be expected with other existing treatments and therefore are clinically significant.").

The Court finds that statistical significance is an important component in establishing the reliability of the clinical data for a person of skill in the art.[21] The bulk of the other evidence on this issue supports that finding. Stevenson's paper, the published account of the Phase 2 results sponsored by Allergan, demonstrates the importance of statistics in drawing conclusions. Stevenson reported that there was no observed dose response, concluded that all tested concentrations performed effectively and safely, and counseled a person of skill to investigate both the 0.05% and 0.1% cyclosporin formulations. That peer-reviewed paper does not go so far as to say that the 0.1% formulation did best, or even that the 0.1% formulation did better than 0.05%. As Allergan's expert agreed, "one point of peer review is to make sure that authors don't overstate their case." Dkt. No. 474, Trial Tr. 55. The Court finds that Stevenson accurately reported the results and formed valid conclusions.

Stevenson's conclusions were corroborated by other persons of skill in the art, including Allergan's own drug developers. Upon presenting the Phase 3 results to the FDA, Allergan explained that the performance of the 0.05% cyclosporin formulation was not surprising because

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[21] The Federal Circuit has noted the importance of statistical significance in evaluating claims of unexpected results in the pharmaceutical arts. See, e.g., In re Efthymiopoulos, 839 F.3d 1375, 1378-79 (Fed. Cir. 2016) (affirming finding of no unexpected results based on study that, among other things, "did not disclose superior results" and reported "findings [that] were admittedly not statistically significant"); Senju Pharm. Co. v. Lupin Ltd., 780 F.3d 1337, 1353 (Fed. Cir. 2015) (affirming district court's finding of no unexpected results where district court was "unpersua[ded]" by study results that "were not statistically significant and merely reported numerical increases that were unsurprising"); McNeil-PPC, Inc. v. L. Perrigo Co., 337 F.3d 1362, 1370 (Fed. Cir. 2003) (district court "properly discounted" evidence of unexpected results because the clinical study results "were inconsistent, not shown to be reproducible, and did not include [particular] comparative data").

the lack of a dose response—i.e., the similar level of efficacy for formulations containing 0.05% or more of cyclosporin—was observed earlier in Phase 2. DTX-1219, at 96.

Dr. Reis, the team leader on the cyclosporin project and clinical research lead, played a decisionmaking role in the clinical trials of Restasis. She testified that after the Phase 2 study, she "concluded, as the clinical lead, as did my team, that the 0.1 percent was the concentration that we would propose to FDA that we were going to take forward for Phase 3 studies." Dkt. No. 470, Trial Tr. 73. She also pointed to a spreadsheet that she created, in which she assigned numbers, 1 through 4, to the performance of each of the cyclosporin concentrations tested in Phase 2 for several efficacy measures. Id. (referring to PTX-172A, at 3). Dr. Reis's aim, however, was simply to identify a concentration that would work to treat dry eye; she was not attempting to use the Phase 2 study as a tool for accurately distinguishing real differences between any two of the tested formulations. Id. at 71; see also Dkt. No. 470, Trial Tr. 147 (Dr. Diane Tang-Liu, one of the named inventors on the Restasis patents, participated in that identification process and testified that "the next logical step [after the Phase 2 results came back] was since the 0.1 formulation looked promising we would like to elevate it for Phase 3 investigation.").

After presenting the FDA with its plan to test the 0.1% formulation in Phase 3, Allergan acknowledged that "[b]ecause we did not show a clear differentiation in effect among the doses [in Phase 2], it was recommended [by the FDA] that we include a lower concentration [0.05% cyclosporin] in one Phase 3 clinical trial to confirm that we have chosen the lowest effective concentration." PTX-39, at 5. Dr. Reis admitted that she was resistant to testing the 0.05% cyclosporin concentration in Phase 3 along with the 0.1% formulation "because it was going to make my job as the clinical scientist considerably more complicated in designing the phase 3

program." Dkt. No. 470, Trial Tr. 77-78. The Court finds that Dr. Reis wanted to avoid testing multiple cyclosporin concentrations in Phase 3 principally because it would make the study design more difficult, not because she believed that the Phase 2 results had demonstrated that the 0.1% cyclosporin formulation had clearly outperformed the 0.05% cyclosporin formulation.

For those reasons, the Court finds that a person of skill reviewing Stevenson alone, or even Stevenson in combination with all the underlying Phase 2 data, would not conclude that the 0.1% cyclosporin/1.25% castor oil formulation was more effective than the 0.05% cyclosporin/0.625% castor oil formulation.

b. Phase 3: the 0.05% cyclosporin/1.25% castor oil formulation performed similarly to 0.1% cyclosporin/1.25% castor oil formulation

Allergan contends that the 0.05% cyclosporin/1.25% castor oil formulation outperformed the 0.1% cyclosporin/1.25% castor oil formulation in the Phase 3 trials, and that the superior performance of the 0.05% cyclosporin/1.25% castor oil formulation was unexpected, particularly in light of the results of the Phase 2 study. But the pooled results from the two Phase 3 studies, like the Phase 2 study results, show that in general the tested 0.1% and 0.05% cyclosporin formulations performed similarly.[22]

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[22] With regard to the unexpected results issue, Allergan has focused on efficacy when comparing the performance of the 0.05% and 0.1% cyclosporin formulations in the Phase 3 studies. Allergan does not suggest that the 0.05% cyclosporin formulation provided unexpected additional safety benefits as compared to the 0.1% cyclosporin formulation. In fact, Allergan presented expert testimony that even the 0.4% cyclosporin formulation from Ding I and the Phase 2 study was extremely safe. The Acheampong reference, a 1998 article by Dr. Andrew Acheampong, one of the named inventors of the Restasis patents, addressed the distribution of cyclosporin following topical dosing and taught that the level of cyclosporin detected in patients' bloodstreams, even after administration of a 0.4% cyclosporin formulation, was only 0.16 nanograms. Andrew Acheampong et al., Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, in David A. Sullivan et al., Lacrimal Gland, Tear Film, and Dry

As Allergan acknowledges, the Phase 3 studies "were designed to make[] a comparison of each active treatment group[] versus vehicle." Dkt. No. 489, at 1. An improvement over the castor-oil-only vehicle was, in fact, what the FDA was looking for in order to approve the drug. See Dkt. No. 494, at 64 (noting that the FDA was looking in the Phase 3 study results for the "replicat[ion]" of results showing "statistically significant improvements over vehicle") (emphasis added); PTX-32, at 5 ("Clinical Studies" section of the Restasis label notes that the Phase 3 studies showed a greater increase in Schirmer scores for Restasis as compared to vehicle). The Phase 3 studies were not designed to find real differences between the 0.05% and 0.1% cyclosporin formulations; rather, they were designed to find real differences between a cyclosporin formulation and the vehicle. The Phase 3 studies, in that respect, are similar to the Phase 2 study, which also was not designed to discover real differences between the 0.05% and 0.1% cyclosporin formulations but was intended to serve as a dose-ranging study to demonstrate safety and some level of efficacy. In any event, like the Phase 2 study, the Phase 3 studies produced results that do not show any real differences between the 0.05% and 0.1% cyclosporin formulations.

The Sall paper analyzed the data from the two Phase 3 studies with respect to a number of efficacy measures. Regarding corneal staining, Sall reported that both the 0.1% and 0.05% cyclosporin formulations showed improved performance over the castor-oil-only vehicle at treatment months 4 and 6, indicated by p-values less than or close to 0.05. See DTX-1017A, at

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Eye Syndromes 2 1004 (1998), DTX-1087, at 7 (table 1). Dr. Perry testified that such a level of cyclosporin dosing, if "given twice a day would probably lead to the minimum toxic level in about 500 years if every part of every drop was totally absorbed, which we know does not occur." Dkt. No. 475, Trial Tr. 107.

635 ($p \leq 0.05$ for both formulations at month 4 and for the 0.05% cyclosporin formulation at month 6; $p = 0.062$ for the 0.1% cyclosporin formulation at month 6).[23] The improvement in corneal staining relative to baseline for both cyclosporin formulations was very similar at all recorded time points. See id. (Fig. 1). That conclusion is supported by the underlying Phase 3 data, which reveals a high p-value of 0.426 for the pair-wise comparison of the two cyclosporin formulations at month 6, the end of the treatment period. DTX-1267, at 112; see also id. (the p-value at month 4 was even higher: 0.713).

In addition to corneal staining, both cyclosporin formulations showed statistically significant improvement compared to baseline at all time points in reducing blurred vision, dryness, sandy/gritty feeling, itching, and photophobia. DTX-1017A, at 636. The 0.05% cyclosporin formulation did significantly better than the castor-oil-only vehicle—but not significantly better than the 0.1% cyclosporin formulation—in reducing blurred vision at month 6. Id. The 0.05% cyclosporin formulation did significantly better than the vehicle in reducing blurred vision and significantly better than the 0.1% cyclosporin formulation at month 3; the 0.05% cyclosporin formulation did significantly better than the vehicle but not significantly better than the 0.1% cyclosporin formulation in reducing blurred vision at months 1, 4, and 6. DTX-1267, at 142.

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[23] The Sall paper was originally published in April 2000. A few months later, the journal printed a correction letter from Dr. Sall. PTX-263 (Sall, "Our Apologies," 107 Ophthalmology 1220 (July 2000)). In his correction letter, Dr. Sall noted a typographical error in the legend of Figure 1, which should state "^{t} P = .062 compared to vehicle" rather than ".62." Dr. Sall also provided a new Figure 4 (Change from Baseline in Blurred Vision) because the version of Figure 4 published in the original paper plotted the same data that was used in Figure 3 (Change from Baseline in Average Daily Use of Artificial Tears).

Meanwhile, the 0.1% cyclosporin formulation demonstrated statistically significant improvement over baseline in reducing pain at all time points, whereas the 0.05% cyclosporin formulation and the vehicle demonstrated statistically significant improvement over baseline in reducing pain only at month 6. DTX-1017A, at 636; see also DTX-1267, at 137. The subjective assessment of physicians regarding the patients' global response to treatment was generally better for the 0.1% cyclosporin formulation at all time points, DTX-1017A, at 636, although that difference was statistically significant as compared to the 0.05% cyclosporin formulation only at month 3, DTX-1267, at 155.

Regarding artificial tear use, both cyclosporin formulations showed a statistically significant decrease from baseline, DTX-1017A, at 636; DTX-1267, at 157.[24] There was a statistically significant decrease in artificial tear use for the 0.05% cyclosporin formulation as compared to the vehicle—but not as compared to the 0.1% cyclosporin formulation—at month 6. DTX-1017A, at 636; DTX-1267, at 158. Neither cyclosporin formulation did significantly better than the vehicle, or significantly better than the other cyclosporin formulation, with respect to OSDI scores and the Subjective Facial Expression Rating Scale. DTX-1017A, at 636; DTX-1267, at 122, 124 (among-group p-values > 0.05).[25]

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[24] The use of artificial tears was considered a measure of the efficacy of the tested formulations based on the assumption that the more effective the formulation, the less the patients would be likely to rely on the use of artificial tears.

[25] Allergan's meta-analysis of the Phase 3 studies (as reflected in the Sall paper) entailed a "[s]tatistical adjustment of *P* values for multiple comparisons . . . to ensure that the experimental-wise error rate was 0.05." DTX-1017A, at 634. "Specifically, a pairwise comparison between either cyclosporin group and vehicle groups is considered statistically significant if and only if, one, the overall comparison among the three groups [vehicle group, 0.05% cyclosporin group, and 0.1% cyclosporin group] is significant at the 0.05 level; and two, the pairwise comparison between cyclosporin and vehicle is significant at the 0.05 level." Id.

Dr. Calman reviewed the Phase 3 data for 21 efficacy measures, as he did for the 14 efficacy measures in Phase 2. Those 21 efficacy measures for Phase 3 were: corneal staining, temporal conjunctival staining, nasal conjunctival staining, the sum of temporal and nasal conjunctival staining, the sum of corneal and conjunctival staining, raw Schirmer scores with anesthesia, categorized Schirmer scores with anesthesia, raw Schirmer scores without anesthesia, categorized Schirmer scores without anesthesia, OSDI score, facial expression subjective rating scale, stinging or burning, itching, sandy or gritty feeling, blurred vision, dryness, light sensitivity, pain, global evaluation of response to treatment, treatment success, and artificial tear use. Dr. Calman looked at those results for all measured time points: 1 month, 3 months, 4 months, and 6 months.[26]

There was no statistical significance in the pair-wise comparisons of the 0.05% and 0.1% formulations for those 21 efficacy measures at all measured time points, with at least three exceptions. First, there was a statistically significant difference favoring the 0.1% formulation over the 0.05% formulation in the global evaluation of response to treatment, but only at month 3. See Dkt. No. 473, Trial Tr. 135; see also DTX-1071, at 49 (Global evaluation of response to treatment was the "evaluation of the overall effect of study medication relative to the qualification visit. The 7-point scale ranged from 0 (completely cleared, no sign or symptom of

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As explained by Dr. Schiffman, "One way in which you protect against making these conclusions that are really unfounded is by controlling the overall p-value. And you can do that first by doing an among-group analysis which determines whether or not any of the groups is different from the rest." Dkt. No. 469, Trial Tr. 59. Therefore, if the "among-group" p-value was not statistically significant (i.e., if the value was greater than 0.05), Allergan did not ascribe any statistical significance to any pair-wise comparisons within that group.

[26] Dr. Calman noted that his summary omitted a few data points, because Allergan's NDA submission did not report results for (i) raw Schirmer scores with anesthesia at months 1 and 4, and (ii) categorized Schirmer scores with anesthesia at months 1 and 4.

disease) to 6 (condition worsened)."). Second, there was a statistically significant difference favoring the 0.05% formulation over the 0.1% formulation in treatment success, but only at month 6. See Dkt. No. 473, Trial Tr. 135; see also DTX-1071, at 50 ("Treatment success was defined as a global response of approximately 90% improvement or better (almost or completely cleared)."). Third, there was a statistically significant difference favoring the 0.05% formulation over the 0.1% formulation in blurred vision, but only at month 3. See DTX-1267, at 142 ($p = 0.008$); see also id. (the difference in blurred vision approached statistical significance at month 4, with a p-value of 0.054, but there was no statistically significant difference at the end of the treatment period, as the p-value for that time point was 0.398).[27]

Despite the lack of analysis of among-group differences and pair-wise comparisons for the raw Schirmer scores, the available data allows for several inferences. First, the raw Schirmer scores without anesthesia collected at months 1, 3, 4, and 6 favored the 0.1% cyclosporin formulation at all time points. Therefore, a pair-wise comparison of the 0.05% and 0.1% cyclosporin formulations for that efficacy measure either would demonstrate no statistical significance or would demonstrate statistical significance favoring the 0.1% cyclosporin formulation. Second, the raw Schirmer scores with anesthesia collected at months 3 and 6 favored the 0.05% cyclosporin formulation at both time points. Therefore, a pair-wise comparison of the 0.05% and 0.1% cyclosporin formulations for that efficacy measure would

[27] Dr. Calman pointed out the first two exceptions in his trial testimony, but he failed to mention the third, regarding blurred vision. That is because Dr. Calman based his analysis on Table 8.6.5 in Allergan's NDA, DTX-1267, at 85, which reports "[t]he statistically significant among-group differences in the meta-analysis" of Allergan's two Phase 3 studies, id. at 84. See Dkt. No. 473, Trial Tr. 133-34. That table does not report the statistically significant difference favoring the 0.05% formulation over the 0.1% formulation in blurred vision.

demonstrate either no statistical significance or statistical significance favoring the 0.05% cyclosporin formulation.

Even assuming that a comparison of the raw Schirmer scores with anesthesia for the two cyclosporin formulations at months 3 and 6 would have resulted in a statistically significant result favoring the 0.05% formulation over the 0.1% formulation, and taking account of the two data points discussed above that favored the 0.05% formulation (subjective assessment of treatment success at month 6 and blurred vision at month 3), only four data points showed a statistically significant difference favoring the 0.05% cyclosporin formulation out of a total of 80 data points. And at least 71 of the 80 total data points showed no statistically significant difference between the two cyclosporin formulations.[28] Thus, the overwhelming bulk of the data (71 out of 80 data points) supports an inference that the two cyclosporin formulations performed similarly, and an even larger portion of the data (76 out of 80 data points) supports an inference that the 0.05% cyclosporin formulation did not perform better than the 0.1% cyclosporin formulation.

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[28] There were 21 efficacy measures and four time points at which values for each of those measures were obtained, resulting in 84 possible data points. But two of the efficacy measures (raw and categorized Schirmer scores with anesthesia) were not observed at two time points (months 1 and 4). Thus, 80 total data points were collected. Of those 80 data points, two data points showed statistical significance favoring the 0.05% cyclosporin formulation (blurred vision at month 3 and treatment success at month 6), and one data point showed statistical significance favoring the 0.1% cyclosporin formulation (global response to treatment at month 3). The statistical significance of six of the data points is unknown. As to four of them (raw Schirmer scores without anesthesia at months 1, 3, 4, and 6), the results were better for the 0.1% formulation, so it can be inferred that those data points would either show no statistical significance or would show statistical significance favoring the 0.1% formulation. As to the other two (raw Schirmer scores with anesthesia at months 3 and 6), the results were better for the 0.05% formulation, so it can be inferred that those data points would either show no statistical significance or would show statistical significance favoring the 0.05% formulation.

The Court does not find that the few data points reflecting statistical significance demonstrate a real difference in effectiveness between the 0.05% and 0.1% cyclosporin formulations. More specifically, the Court does not find that the four individual data points (at most) that showed statistical significance in favor of the 0.05% cyclosporin formulation indicate a real difference in effectiveness favoring the 0.05% over the 0.1% cyclosporin formulation, as Allergan contends. In fact, it appears that Allergan never performed pair-wise comparisons for two of those four data points—the raw Schirmer scores with anesthesia at months 3 and 6. Dr. Bloch did perform the relevant calculations and found no statistically significant differences favoring the 0.05% cyclosporin formulation over the 0.1% cyclosporin formulation. Dkt. No. 476, at 67-73 (Dr. Bloch calculated p-values for the pair-wise comparisons between the 0.05% and 0.1% cyclosporin formulations for raw Schirmer scores both with and without anesthesia, and for categorized Schirmer scores both with and without anesthesia, at all time points in each of the Phase 3 studies; he found only two points of statistical significance, both favoring the 0.1% formulation).

Instead of viewing the results in their totality, Allergan relies heavily on one particular outcome measure: the categorized Schirmer tear test scores with anesthesia. See Dkt. No. 494 (Allergan's Post-Trial Findings of Fact and Conclusions of Law), at 62, 70, 71, 78, 80, 81, 88-89 (citing DTX-1017A, at Fig. 2). On that one endpoint, the performance of the 0.05% cyclosporin formulation was better, as a matter of statistical significance, than the castor-oil-only vehicle at both measured time points, month 3 and month 6. DTX-1017A, at 635 (Fig. 2); DTX-1267, at 147 ($p = 0.009$ at month 3; $p < 0.001$ at month 6). But the difference in the performance of the 0.05% cyclosporin formulation compared to the 0.1% cyclosporin formulation on that test was

not statistically significant at either time point. DTX-1267, at 147 ($p = 0.076$ at month 3; $p = 0.258$ at month 6).

Allergan points out that, for the categorized Schirmer tear test scores with anesthesia, the p-value for the pair-wise comparison between the 0.05% and 0.1% cyclosporin formulations at month 3 was 0.076. While not statistically significant, that p-value approached statistical significance. DTX-1267, at 147. Even granting some flexibility to the conventional line of "statistical significance" at 0.05, however, the Court is not persuaded that the single cherry-picked data point of categorized Schirmer scores with anesthesia at month 3 demonstrates a real difference in efficacy between the two cyclosporin formulations, for several reasons.

First, at the end of the treatment period (month 6), the categorized Schirmer tear test scores with anesthesia for the 0.05% and 0.1% cyclosporin formulations were both statistically significant as compared to the vehicle. DTX-1267, at 147 ($p < 0.01$ for both pair-wise comparisons to the vehicle). In addition, there was no statistically significant difference between the two cyclosporin formulations at the end of the treatment period; rather, the pair-wise comparison produced a p-value greater than 0.25. Id.

Second, for categorized Schirmer tear test scores without anesthesia, the 0.1% cyclosporin formulation performed better than the 0.05% cyclosporin formulation at all time points, although there was no statistically significant difference between those two formulations. See DTX-1267, at 144; see also Dkt. No. 469, Trial Tr. 60. That is the same result as seen in Phase 2 at all of the testing times. See PTX-16D, at AGN_RES0012944-45 (the 0.1% cyclosporin formulation did better than the 0.05% cyclosporin formulation in Phase 2 for categorized Schirmer tear test scores without anesthesia, although pair-wise comparisons of the

0.05% and 0.1% cyclosporin formulations are not available or are not statistically significant).[29] Allergan has not adequately explained why the Court should compare categorized Schirmer scores without anesthesia in the Phase 2 study, to categorized Schirmer scores with anesthesia in the Phase 3 study, when the point is to understand whether the results in Phase 3 were surprising in light of the results in Phase 2. Schirmer tests with anesthesia were not performed in Phase 2, but both types of tests were performed in the Phase 3 studies. Allergan could have conducted, but chose not to conduct, a direct comparison of the categorized Schirmer scores without anesthesia. That direct comparison shows similar results in both phases: The 0.1% cyclosporin formulation performed better than the 0.05% cyclosporin formulation at all time points in both phase 2, see DTX-1267, at 144, and phase 3, see PTX-16D, at AGN_RES0012944.

Third, the underlying Phase 3 raw Schirmer scores with anesthesia at month 3 tell a different story than the derived Phase 3 categorized Schirmer scores with anesthesia at month 3. The raw Schirmer scores are measured in millimeters of tearing produced in 5 minutes. To produce categorized Schirmer scores, the raw Schirmer scores are assigned to a numbered category, see DTX-1267, at 146:

Raw Schirmer Score (mm/5mins)	**Categorized Schirmer Score**
0-3	1
4-6	2
7-10	3
11-14	4
> 14	5

[29] See note 14 supra.

In the pooled Phase 3 studies, the mean raw Schirmer scores increased (i.e., were positive) for all tested formulations: the mean increase in Schirmer scores for the 0.05% cyclosporin formulation was 2.57; the mean increase in Schirmer scores for the 0.1% cyclosporin formulation was 2.18; and the mean increase in Schirmer scores for the castor-oil-only vehicle was 1.58. DTX-1267, at 151. Even though all raw Schirmer scores increased at month 3, the mean categorized Schirmer scores for that month were, oddly, negative for the 0.1% cyclosporin formulation and for the vehicle. See DTX-1017A, at 635 & Fig. 2; DTX-1267, at 146. In other words, the act of categorizing, or "binning," the raw Schirmer scores skewed the numbers and thus misrepresented the actual results, falsely indicating that there had been a decrease in the mean Schirmer scores for the 0.1% cyclosporin formulation. Dkt. No. 473, Trial Tr. 142-43; Dkt. No. 476, Trial Tr. 66-67.

Two other points are worth noting:

First, Allergan highlights Figure 3 in Sall, which depicts the changes from baseline in blurred vision for the three tested formulations over the four reporting periods. That figure, however, does little to support Allergan's claim of unexpected results. The figure shows that the improved performance of the 0.05% formulation was statistically significant as compared to the vehicle at all time points, and that the improved performance of the 0.1% formulation was not statistically significant as compared to the vehicle at all time points. DTX-1017A, at 636 & Fig. 3. But the figure does not show the pair-wise comparisons of the two cyclosporin formulations. Those pair-wise comparisons have p-values of 0.111 (month 1), 0.008 (month 3), 0.054 (month 4), and 0.398 (month 6). DTX-1267, at 142. The performance of the 0.05% formulation was therefore statistically significant as compared to the 0.1% formulation at month 3, it approached

statistical significance at month 4, and it was very far from statistical significance at month 6, the end of the treatment period. The Court finds that some statistical significance at one or two time points on one efficacy measure out of many tested is not sufficient to show that the 0.05% formulation was more effective than the 0.1% formulation.[30]

Second, Sall reported that both cyclosporin formulations did well as compared to the castor-oil-only vehicle, but did not conclude that the 0.05% cyclosporin formulation outperformed the 0.1% cyclosporin formulation. Sall stated that, "[i]n 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 the vehicle alone in two objective signs of dry eye disease (corneal staining and categorized Schirmer scores), whereas treatment with CsA 0.05%, resulted in significantly greater improvements than the vehicle ($P \leq 0.05$) in three subjective parameters (blurred vision, use of lubricating eye drops, and the physician's evaluation of global response to treatment)." DTX-1017A, at 637; accord id. at 631.

While noting that the results for the 0.05% formulation were significantly better than for the castor-oil-only vehicle on those three subjective efficacy measures, Sall did not find that the results for the 0.05% formulation were significantly better than for the 0.1% formulation on those measures. And even the statistically significant difference between the 0.05% formulation and the castor-oil vehicle, according to Sall, was expected: "The improvements in the subjective measures of blurred vision, physician's global assessment, and the decreased need for use of artificial tears are consistent with the improvements in subjective measures seen in previous

[30] The Court is even less persuaded by Figure 4 in Sall, which shows no statistically significant difference between the two cyclosporin formulations for artificial tear use at any time point, and which reports a statistically significant difference between the 0.05% cyclosporin formulation and the vehicle for only one time point. DTX-1017A, at 636 & Fig. 4.

studies of the use of topical [cyclosporin A] in dry eye disease." DTX-1017A, at 637 (citing Stevenson, among other references).

In sum, there is a dearth of evidence showing any real difference between the efficacy of the 0.05% and 0.1% cyclosporin formulations in Phase 2, as presented in Stevenson, and in Phase 3, as presented in Sall. A person of skill reviewing those papers would come to the conclusion that neither formulation was more effective than the other in Phase 2. That person of skill would reach the same conclusion for Phase 3.

Even reviewing all of the underlying data in Allergan's NDA submission, including internal data that was not reported in Stevenson and Sall, a person of skill would reach the same conclusions. The table below summarizes the pair-wise comparisons of the 0.05% and 0.1% cyclosporin formulations for the majority of the overlapping efficacy measures in Phase 2 and Phase 3, measured at the end of the Phase 2 treatment period (month 3), at the corresponding time point in Phase 3 (month 3), and at the end of the Phase 3 treatment period (month 6). As indicated in the table, there were only two categories that produced statistically significant results: OSDI in Phase 2 (which favored the 0.1% cyclosporin formulation) and blurred vision in Phase 3 (which favored the 0.05% cyclosporin formulation).[31]

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[31] Although this table was created by the Court, the entries in the table were collected or derived from evidence at the trial: PTX-16D, at AGN_RES0012941-42, AGN_RES0012947, AGN_RES0012949, AGN_RES0012952-55, AGN_RES0012984, AGN_RES0012994-13001, AGN_RES0013005-06, AGN_RES0013012; DTX-1191, at 248, 250, 267, 275-78; DTX-1267, at 111-12, 114, 116, 122, 128, 130, 132, 134, 137, 139, 141-42, 144, 146-47, 149, 151, 158. P-values less than or equal to 0.05 ("statistically significant") are shaded gray. Where the table indicates "No" statistical significance but a p-value is not specified, the among-group p-value was greater than 0.05 and no pair-wise comparisons were calculated. See DTX-1017A, at 634; Dkt. No. 469, Trial Tr. 59-60; see also Dkt. No. 463, Trial Tr. 129-30. Where the table does not report anything, no among-group p-value and no pair-wise comparisons were calculated.

Efficacy Measure	Phase 2: 0.05% versus 0.1% Month 3	Phase 3 (pooled): 0.05% versus 0.1% Month 3	Phase 3 (pooled): 0.05% versus 0.1% Month 6
Categorized Schirmer Scores (without anesthesia)	--	No	No
Categorized Schirmer Scores (with anesthesia)	--	No (p = 0.076)	No (p = 0.258)
Schirmer Scores (without anesthesia)	No (p = 0.834)	--	--
Schirmer Scores (with anesthesia)	--	--	--
Corneal Staining	No (p = 0.112)	No	No (p = 0.426)
Conjunctival Staining (Nasal)	No (p = 0.649)	No	No
Conjunctival Staining (Temporal)	No (p = 0.113)	No	No
Dryness	No (p = 0.654)	No	No
Sandy / Gritty Feeling	No (p = 0.225)	No	No
Burning / Stinging	No (p = 0.589)	No	No
Pain	No (p = 0.717)	No	No
Itching	No (p = 0.932)	No	No

Sensitivity to Light	No (p = 0.212)	No	No
Blurred Vision	No (p = 0.065)	Yes (favors 0.05%) (p = 0.008)	No (p = 0.398)
OSDI	Yes (favors 0.1%) (p = 0.049)	No	No
Artificial Tear Use	No (p = 0.133)	No	No (p = 0.122)

2. Dr. Schiffman's declaration presented no additional evidence to support Allergan's claim of unexpected results

Based on a review of the evidence discussed above, the Court does not credit the assertions made in Dr. Schiffman's declaration that was submitted to the PTO to obtain allowance of the Restasis patents. See PTX-2A. Dr. Schiffman touted the Schirmer tear test scores and corneal staining scores as "key objective measures for determining dry eye or keratoconjunctivitis sicca disease severity." Id. at 553, ¶ 7. He then made several important assertions about the data:

a) In Phase 2, the 0.1% cyclosporin formulation "demonstrated a greater decrease in corneal staining than the 0.05%" cyclosporin formulation, and the 0.1% cyclosporin formulation "demonstrated a greater increase in Schirmer score (tear production) at week 12 than any other formulation tested, including the 0.05%" cyclosporin formulation, id. ¶ 7 (emphasis in original; and

b) In Phase 3, the 0.05% cyclosporin formulation "was unexpectedly superior to the 0.10%" cyclosporin formulation, "exhibit[ing] a comparable or greater decrease in corneal staining score (see Exhibit D, Figure 1), a greater increase in Schirmer Score (see Exhibit D, Figure 2), an improvement in the common dry eye/keratoconjunctivitis sicca symptom of blurred vision (see Exhibit D, Figure 3) and a greater decrease in the number of artificial tears used by patients (see Exhibit D, Figure 4)," id. at 555, ¶ 16.

Dr. Schiffman's declaration covered some of the same evidence that was disclosed in the Sall and Stevenson papers, but without accounting for the lack of statistical significance of much of the data on which he relied. The figures that were included in his declaration (Exhibit D, Figs. 1-4) were taken directly from the Sall paper, but omitted all error bars and p-values. Dr. Schiffman explained his omission of any reference to statistical significance as follows: "I think we're making – in a sense, we're trying to make too much out of statistical techniques when the bigger picture is – is – is really sufficient, I think. [0].05 performed better in Phase 3. That, to me, is not really so much up to debate." Dkt. No. 469, Trial Tr. at 124; see also id. at 123 (Dr. Schiffman, "That there are no p-values for me then and now mean nothing.").

The Court has already rejected the view that it is not necessary to conduct statistical analysis of the clinical trial data in order to determine whether the performance of the 0.05% cyclosporin formulation in the Phase 3 trials qualifies as "critical" or "unexpected" for purposes of obviousness analysis. Importantly, in the Court's view, none of the pair-wise comparisons between the two cyclosporin formulations for corneal staining and Schirmer scores in the Phase 2 study or the pooled Phase 3 studies demonstrated statistical significance at any time point, and many of the p-values for the pair-wise comparisons were very high. See, e.g., PTX-16D, at AGN_RES0012945 (the p-value for a comparison of Schirmer scores without anesthesia in Phase 2, the only p-value regarding Schirmer scores that was calculated in Phase 2, was 0.651 at week 4, 0.790 at week 8, and 0.834 at week 12); DTX-1267, at 112 (the p-value for a comparison of corneal staining in Phase 3 was 0.713 at month 4 and 0.426 at month 6).

Despite the statistical analyses showing that any observed difference in raw numbers between the cyclosporin formulations was likely the result of random chance, Dr. Schiffman directly compared the raw numbers and inferred "real" differences in efficacy based on those

comparisons. Comparing the Schirmer scores without anesthesia in Phase 2, he determined that the 0.1% cyclosporin/1.25% castor oil formulation was four times as effective as the 0.05% cyclosporin/0.625% castor oil formulation. PTX-2A, at 555-56, ¶ 18. Comparing the Schirmer scores with anesthesia in Phase 3, he determined that the 0.05% cyclosporin/1.25% castor oil formulation was up to twice as effective as the 0.1% cyclosporin/1.25% castor oil formulation. Id. Comparing the corneal staining data, he determined that the 0.1% cyclosporin/1.25% castor oil formulation was four times as effective as the 0.05% cyclosporin/0.625% castor oil formulation in Phase 2, and that the 0.05%/1.25% castor oil cyclosporin formulation was equally effective as compared to the 0.1% cyclosporin/1.25% castor oil formulation in Phase 3. Id. Based on those assessments, Dr. Schiffman represented to the PTO that the 0.05% cyclosporin/1.25% castor oil formulation in Phase 3 was four to eight times as effective in increasing Schirmer scores as the 0.05% cyclosporin/0.625% castor oil formulation in Phase 2, and that the 0.05% cyclosporin/1.25% castor oil formulation in Phase 3 was four times as effective in decreasing corneal staining as the 0.05% cyclosporin/0.625% castor oil formulation in Phase 2. That outcome, he said "was clearly a very surprising result" and "unexpectedly critical for therapeutic effectiveness in the treatment of dry eye/keratoconjunctivitis sicca." Id. at 556, ¶¶ 19-20 (emphasis in original).

In addition to the dubious validity of those inferences from the direct comparison of raw numbers given the high associated p-values, Dr. Schiffman did not disclose in his declaration to the PTO that he was comparing different Schirmer tear test scores: test scores without anesthesia in Phase 2, versus test scores with anesthesia in Phase 3. As noted previously, the Schirmer tear test results without anesthesia in Phase 3 showed a trend similar to that of the Schirmer tear test results without anesthesia in Phase 2, in that both favored the 0.1% cyclosporin formulation.

Only the Schirmer tear test results with anesthesia in Phase 3 significantly favored the 0.05% cyclosporin formulation; that was the data point that Dr. Schiffman chose to rely upon in his declaration to support his contention that "the claimed formulation and method demonstrated an *8-fold* increase in relative efficacy" as compared to the 0.1% formulation. PTX-2, at 556, at ¶ 19 (emphasis in original). It was therefore only by comparing the results of two different types of tests that Dr. Schiffman was able to produce a significantly distorted picture suggesting that the 0.05% cyclosporin/1.25% castor oil formulation in Phase 3 was much more effective than the 0.05% cyclosporin/0.625% castor oil formulation in Phase 2.

Moreover, the method that Dr. Schiffman used in his declaration to calculate the differences in efficacy between the 0.05% and 0.1% cyclosporin formulations exaggerated the differences in the raw values between the two. As Dr. Schiffman explained at trial, he first compared the median change from baseline in corneal staining scores at week 12 for the 0.05% and 0.1% cyclosporin formulations in the Phase 2 study. He calculated that the change from baseline for the 0.05 formulation was approximately one-quarter as large as the change from baseline for the 0.1% formulation. He then conducted a similar comparison of the 0.05% and 0.1% formulations in Phase 2 with regard to the median change in Schirmer scores without anesthesia, again concluding that the change from baseline was approximately one-quarter as large for the 0.05% formulation as for the 0.1% formulation. He then performed the same calculation for corneal staining and Schirmer scores without anesthesia for each of the two Phase 3 studies. The median improvement in the corneal staining scores for both Phase 3 studies was roughly the same, as was the median improvement in the Schirmer scores for the second Phase 3 study. However, Dr. Schiffman calculated the improvement in Schirmer scores for the first

Phase 3 study as being approximately twice as great for the 0.05% formulation as for the 0.1% formulation.

Based on those calculations, Dr. Schiffman presented the following table to the PTO as an attachment to his declaration:

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

The calculations in Dr. Schiffman's table are misleading in several respects. First, the use of ratios of the degree of improvement tends to overstate the difference between the results in the compared parameters. Thus, for example, Dr. Schiffman's statement that there was an "8-fold improvement" between the Schirmer tear test scores in the Phase 2 study and in the first study in Phase 3 is misleading because it is based on a calculation of the ratio of the differences between the improvement from baseline for the 0.05% and 0.1% cyclosporin formulations for the two studies. Even though the actual difference in the median improvement in Schirmer scores for the 0.05% and 0.1% formulations in Phase 2 was only about 1.5 millimeters, the use of ratios to represent the difference suggested that the difference was 4:1 in favor of the 0.1% formulation. Similarly, although the difference between the 0.05% and 0.1% formulations in the first study of Phase 3 was not dramatic, depicting that difference as a ratio of the differences from baseline tended to exaggerate its

significance by suggesting that the 0.05% formulation was twice as effective as the 0.1% formulation. Dr. Schiffman then calculated the ratio of the two ratios (2/.25), deriving a ratio of 8:1, which again exaggerated the difference between the 0.05% and 0.1% formulations as measured in the Phase 2 and Phase 3, suggesting that the 0.05% cyclosporin/1.25% castor oil formulation performed eight times as well in the first study of Phase 3 as the 0.05% cyclosporin/0.625% castor oil formulation in the Phase 2 study.[32]

The inherent flaw in using a "ratio of ratios," as Dr. Schiffman did, can be illustrated by a simple example. Suppose that the baseline value on some metric was 10.00. Suppose further that the Phase 2 data showed an improvement to 10.01 for the 0.05% cyclosporin/0.625% castor oil formulation and an improvement to 10.03 for the 0.1% cyclosporin/1.25% castor oil formulation. Suppose further that the Phase 3 data showed an improvement to 10.01 for the 0.1% cyclosporin/1.25% castor oil formulation and an improvement to 10.03 for the 0.05%/1.25% castor oil cyclosporin formulation. Finally, suppose that statistical analysis showed that none of those small variations in performance were statistically significant, but were likely just the product of experimental noise. Nonetheless, the ratio of the measured improvements in the metric for the 0.1% cyclosporin/1.25% castor oil formulation to the 0.05%

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[32] Dr. Schiffman used the median, instead of the mean, to calculate those changes from baseline. Dkt. No. 469, Trial Tr. 72. As Dr. Bloch explained, the use of medians instead of means is inadvisable because "you can do statistical analysis on means and determine whether things are statistically significant. You can't do that with medians." Dkt. No. 473, Trial Tr. 158. Dr. Schiffman testified that he used medians because the sample sizes in Phase 2 were very small and, in that context, means are more sensitive to outliers. See Dkt. No. 469, Trial Tr. 72. The Court does not need to reach the issue of whether it was improper for Dr. Schiffman to use medians instead of means, given the other problems with Dr. Schiffman's analysis. But the Court notes that Dr. Schiffman's declaration to the Patent Office does not disclose that he used medians instead of means in the calculation upon which he primarily relied. See Dkt. No. PTX-2A, at 555-56, 573-76.

cyclosporin/0.625% castor oil formulation in Phase 2 would 3:1, and the ratio of the measured improvements in the metric for the 0.1% cyclosporin/1.25% castor oil formulation to the 0.05% cyclosporin/1.25% castor oil formulation in Phase 3 would be 1:3. The ratio of those two ratios would be 9:1. Any conclusion from the "ratio of ratios" that there was a nine-fold relative improvement in performance by the 0.05% formulation in Phase 3 over Phase 2 would obviously be spurious.

Second, Dr. Schiffman's calculations ignore the fact that the Phase 2 study was quite small and that the difference in the raw numbers for the 0.05% cyclosporin formulation compared to the 0.1% formulation on some metrics, including Schirmer scores, were not statistically significant. Yet by relying on ratios derived from those raw numbers, Dr. Schiffman was able to present a picture in which it appeared that the 0.1% formulation substantially outperformed the 0.05% formulation in Phase 2, which is not the picture that emerges from a more comprehensive examination of the results of that study, as the Stevenson paper makes clear.

Third, Dr. Schiffman selected only two categories to compare the performance of the 0.05% and 0.1% cyclosporin formulations. In other categories for the Phase 2 studies, the 0.05% formulation did better than the 0.1% formulation. In order to make an appropriate assessment of the Phase 2 study data, it is necessary to view that data globally, not to select the data points that are most favorable to a particular desired outcome.[33]

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[33] The Court further discounts Dr. Schiffman's conclusions to the extent that he relies on Sall's Figure 2 (Exhibit D, Figure 2 in Dr. Schiffman's declaration) to show a difference in Schirmer score improvement between the two Phase 3 cyclosporin formulations. Dr. Schiffman's figure is faulty for the reasons previously set forth in the discussion of Sall's Figure

Finally, while Dr. Schiffman presented the PTO with evidence from the Sall paper to show that the Phase 3 results were surprising, he did not note in his declaration that the evidence was taken from Sall, which had been published 13 years earlier, and three years before the priority date for the Restasis patents. A major flaw in Dr. Schiffman's presentation was thus that, even if the results reported in Sall would have been surprising at the time the Phase 3 trials were conducted, those results were publicly known before the invention. For that reason, the results shown in the Sall article were prior art to the Restasis patents and cannot serve as a basis for finding that the Phase 3 studies would have been unexpected to a person of skill in the art as of the Restasis patents' priority date.

To the extent that Allergan relies on Dr. Schiffman's presentation to the PTO, see Allergan's Post-Trial Findings of Fact and Conclusions of Law, Dkt. No. 494, ¶¶ 216, 217, and the fact that the examiner concluded that unexpected results had been shown, see id. ¶¶ 150, 171, the Court finds that the presentation made to the examiner in 2013, including Dr. Schiffman's declaration and the accompanying exhibits, painted a false picture of the comparative results of the Phase 2 and Phase 3 trials. In addition, that presentation created the misleading perception that the evidence that Dr. Schiffman relied on to show unexpected results was not known at the time of the invention. Accordingly, the Court regards the examiner's finding of unexpected results to be entitled to no weight, based as it was on evidence that did not accurately depict the

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2, as well as Dr. Schiffman's omission of the error bars and p-values in his reproduction of that figure in his declaration.

comparative results of the two Allergan studies and that was, in any event, disclosed in the prior art.[34]

3. The FDA's Medical Review does not support Allergan's claim of unexpected results

Allergan relies in part on a 2002 FDA Medical Review of the Restasis NDA in which the FDA analyzed some of the data from the Phase 3 studies. PTX-963. Focusing on specific populations identified within the study and the number of those patients who achieved an increase in Schirmer tear test scores of 10 millimeters or more, the FDA noted that all of the population groups "trend toward higher responder rates for the 0.05% cyclosporine treatment group." Id. at 26, 29. In two of the groups, the FDA concluded that the responder rates "are statistically significant favoring 0.05% cyclosporine in both trials." Id. The FDA's analysis and statement regarding statistical significance were directed to an among-group analysis of the performance of the 0.05% cyclosporin formulation, the 0.1% cyclosporin formulation, and the castor-oil-only vehicle.

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[34] Allergan contends that the defendants' "clear and convincing burden is more difficult to meet" because "the art that is cited by [d]efendants was before the PTO during prosecution." Dkt. No. 494, at 130. In an earlier order entered in this case, the Court acknowledged that "the Sall article was incorporated by reference in each of the applications" for the asserted patents and "was hardly concealed from the examiner." Dkt. No. 250, at 10. Although the Sall article was, in that sense, before the PTO, the prosecution history indicates that the examiner did not consider Sall—or Stevenson, which was also incorporated in the applications—when evaluating Dr. Schiffman's declaration and deciding to issue the notice of allowance. The Court therefore does not accord the PTO decision to allow the patents any additional weight based merely on the fact that Sall and Stevenson were not hidden from the examiner. See OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698, 704-05 (Fed. Cir. 2012) (rejecting argument that challenger faced an "enhanced burden" in that situation, because the burden of clear and convincing evidence remains unchanged); Tokai Corp. v. Easton Enters., 632 F.3d 1358, 1367 (Fed. Cir. 2011). Even if, as Allergan contends, the defendants' burden was "more difficult to meet," the Court finds that the evidence the defendants have put forth, and in particular the evidence demonstrating the specific flaws in Dr. Schiffman's declaration, would satisfy that burden.

While the FDA accurately described the data and the conclusions that can be reached from that data, the point of the FDA's analysis was to show that the 0.05% cyclosporin formulation performed significantly better than the castor-oil-only vehicle in those studies. The FDA did not conduct a pair-wise comparison between the 0.05% cyclosporin formulation and the 0.1% formulation, and it drew no statistical conclusions from the relative performance of the two cyclosporin formulations. For example, the FDA pointed out that the results of the second of the two Phase 3 studies were statistically significant and favored the 0.05% cyclosporin formulation. But the raw numbers for that study suggest that the statistical significance derives from the difference between the 0.05% cyclosporin formulation and the vehicle, not from the relative performance of the two cyclosporin formulations. The raw numbers for that study show that 12% of the patients who received the 0.05% cyclosporin formulation achieved an increase of 10 millimeters or more, compared to 9% of those who received the 0.1% cyclosporin formulation, and only 2% of those who received the vehicle. Id. at 26. Allergan points to the first of the Phase 3 studies, which demonstrated better numbers for the 0.05% cyclosporin formulation. Again, however, no pair-wise comparison between the two cyclosporin formulations was performed. And when viewing those results together with the results of the second phase 3 study, one cannot draw a conclusion based on the numbers alone that there was a statistically significant difference between the 0.1% cyclosporin formulation and the 0.05% cyclosporin formulation. The Court therefore finds that the single set of results in the first Phase 3 study does not support a finding that the Restasis formulation, as compared to the 0.1% cyclosporin formulation, demonstrated unexpected results.

While the FDA observed that the trend of the data favored the 0.05% formulation, the agency's principal objective was to determine whether one of the tested formulations showed

efficacy against the vehicle, and its statistical analysis was therefore directed to that issue, not to a pair-wise comparison of the two cyclosporin formulations. For that reason, the FDA's Medical Review does not provide significant support for Allergan's assertion that the results of the Phase 3 studies would have been unexpected.

4. The success of Restasis would not have been surprising to a person of skill in the art in 2003.

Several Allergan employees testified that they were surprised that the Restasis formulation did well in the Phase 3 results. See Dkt. No. 469, Trial Tr. 69 (Dr. Schiffman); Dkt. No. 470, Trial Tr. 88 (Dr. Tang-Liu); id. at 130-31 (Dr. Reis). In assessing that testimony, it is important to note, as discussed in connection with Dr. Schiffman's declaration, that Sall's account of the Phase 3 results was in the prior art. Thus, while the Allergan employees may have been surprised upon learning of the Phase 3 results in the late 1990s, the question before the Court is the very different question whether a person of ordinary skill would have been surprised about the success of Restasis in light of all of the prior art in 2003, including the results of the Phase 3 studies, as reported in Sall.

The Court finds that the relative success of the 0.05% cyclosporin formulation would not have been a surprise to persons of ordinary skill by the 2003 priority date for the Restasis patents, in light of the disclosures in the prior art by that time, including the Sall paper. Because the only material fact omitted from the Sall paper was the percentage of castor oil in the test formulations, Allergan's "unexpected results" argument must rely entirely on the allegedly unexpected result that increasing the amount of castor oil in the 0.05% formulation between Phase 2 and Phase 3 did not significantly handicap that formulation. A close analysis of the

evidence leads to the conclusion that a person of ordinary skill in the art in 2003 would not have found that outcome to be unexpected.

Allergan argues that even if the Restasis formulation did not outperform the 0.1% cyclosporin/1.25% castor oil emulsion in the Phase 3 trials, the Restasis formulation at least performed similarly. That similar performance was a surprising result, according to Allergan, because a person of skill would have expected that increasing the amount of castor oil in the 0.05% castor oil formulation from 0.625% (as in Phase 2) to 1.25% (as in Phase 3) would "overwhelm" the cyclosporin and make the 0.05% formulation ineffective. See Dkt. No. 470, Trial Tr. 80 (Dr. Reis).

In pressing that argument, Allergan relies on the testimony of various witnesses, including its expert witness in pharmaceutical chemistry, Dr. Thorsteinn Loftsson. Dr. Loftsson testified that a person of skill in the art would expect that increasing the amount of castor oil in an emulsion such as Restasis would decrease the bioavailability of the active cyclosporin dissolved in the castor oil. Dr. Loftsson explained that, in the context of cyclosporin oil-in-water emulsions, bioavailability refers to the fraction of the drug that goes into the ocular tissue. Dkt. No. 474, Trial Tr. 82. The portion of the drug that is not absorbed into the ocular tissue "is washed down into the nose and is absorbed into general blood circulation." Id. Drug formulators aim to increase bioavailability both because it may increase efficacy and because it decreases the amount of drug absorbed into the circulatory system, which can cause adverse side effects. Id. at 82-83.

Dr. Loftsson then discussed why increasing the amount of castor oil in the cyclosporin emulsion would decrease the bioavailability of the cyclosporin. He explained that cyclosporin dissolved in castor oil has a particular thermodynamic activity, which refers to "the ability of the

drug [cyclosporin] to leave the vehicle [castor oil emulsion] and go into the ocular tissue." Dkt. No. 474, Trial Tr. 83. "[I]f you add too much castor oil, more than you need, then . . . the thermodynamics of the drug will go down. The drug will have less tendency to leave the vehicle and go into the ocular tissue." Id. at 84.

According to Dr. Loftsson, thermodynamic activity and bioavailability are directly related: "If you have high thermodynamic activity, the drug has great tendency to leave the vehicle, go into the tissue. This will mean that high thermodynamic activity will result in high bioavailability." Dkt. No. 474, at 84. For that reason, he explained, "[y]ou don't want to add too much oil to your vehicle." Dkt. No. 474, Trial Tr. 83-84. Rather, "you want to add just enough [oil] to solubilize the drug and keep it in solution through the shelf life of the product. . . . So in general, if you think about this in this cyclosporin/castor oil ratio, you want to keep that ratio high, not low." Id. Allergan formulator Dr. Orest Olejnik testified similarly that "[y]ou would want to be at the high level" of the range of acceptable cyclosporin-to-castor-oil ratios "to try to get as much bioavailability of the cyclosporin into the eye." Dkt. No. 469, Trial Tr. 163; see also id. at 158 (Dr. Olejnik explaining that increasing castor oil in the formulation "is going to give you a lower thermodynamic activity," which will negatively impact the drug's bioavailability); Dkt. No. 475, Trial Tr. 103-04 (similar testimony from Allergan clinical expert Dr. Perry).

In support of the same point, Allergan offered testimony from Dr. Tang-Liu, who was the head of the pharmacokinetics department at Allergan. Dr. Tang-Liu performed pharmacokinetic studies in rabbits before the Phase 2 and Phase 3 clinical trials of Restasis. See PTX-16G; PTX-16H. Those studies tested the relationship between the amount of cyclosporin administered and the level of cyclosporin detected in rabbit eye tissue after administration. Dkt. No. 470, Trial Tr. 140-151.

In the first of those studies, Dr. Tang-Liu tested formulations with varying amounts of cyclosporin but a cyclosporin-to-castor-oil ratio of 0.08. Although the dose-response effect among the formulations was not proportional (i.e., doubling the concentration of cyclosporin administered did not result in a doubling of the amount of cyclosporin in the tissues), Dr. Tang-Liu observed a dose-dependent effect (an increase in the amount of cyclosporin in the tissue with increases in the administered dose) between the formulations containing 0.05% and 0.2% cyclosporin. Dkt. No. 470, Trial Tr. 142-43.

In the second study, Dr. Tang-Liu tested the two Phase 3 cyclosporin formulations: the 0.05% cyclosporin/1.25% castor oil formulation (with a cyclosporin-to-castor-oil ratio of 0.04) and the 0.1% cyclosporin/1.25% castor oil formulation (with a cyclosporin-to-castor-oil ratio of 0.08). See PTX-16H. In that study, the dose-response effect was more than dose-proportional; that is, more than twice the amount of cyclosporin was detected in the rabbit eye tissue for the second formulation than for the first. See Dkt. No. 470, Trial Tr. 150. Dr. Tang-Liu believed that the increased castor oil in the 0.05% cyclosporin formulation (resulting in a 0.04 ratio of cyclosporin to castor oil) caused a decrease in the thermodynamic activity of the cyclosporin and thus a decrease in ocular tissue exposure to the drug. Id. at 150-51.

For that reason, Dr. Tang-Liu stated that she was "puzzled, surprised, and sort of troubled" when she saw the Restasis Phase 3 clinical trial results, which showed that the two cyclosporin formulations (0.05% cyclosporin in 1.25% castor oil, and 0.1% cyclosporin in 1.25% castor oil) performed similarly in human clinical trials. Dkt. No. 470, Trial Tr. 151. Dr. Tang-Liu then conducted an additional pharmacokinetic study, but the results she obtained from that study were consistent with those obtained from her earlier studies. See id. at 152-56 (referring to PTX-108). She testified that neither set of studies "match[ed] up with how the Restasis

formulation performed in the clinic." Id. at 156-57. Dr. Tang-Liu admitted that she did not know why the pharmacokinetic and clinical results were inconsistent, and that she was never "able to figure out why Restasis works the way it does." Id. at 131.

Allergan's evidence, however, does not tell the full story. First, thermodynamic activity is not the sole determinant of bioavailability. As the defendants' expert, Dr. Justin Hanes, testified, "many things . . . go into determining what will be the bioavailability," including the "concentration driving force," "the area over which you would deliver the drug," and "how much time you give for the drug on the surface"—i.e., ocular residence time. Dkt. No. 471, Trial Tr. 187-88. "[S]o it's incorrect to equate thermodynamic activity with bioavailability." Id.

Second, bioavailability does not necessarily determine clinical efficacy. In order for an increase in bioavailability from a lower to a higher level to increase the efficacy of a drug, there must be a dose response between those two levels. If there is no dose response, a greater level of bioavailability will have no additional therapeutic effect. As defendants' expert Dr. Calman explained, "getting more drug into the tissue will get you more effect. But if you're over a threshold level, that may not be the case." Dkt. No. 473, Trial Tr. 67. As seen in the Phase 2 study and reported in the Stevenson paper, there was a lack of a dose response for the tested cyclosporin formulations. DTX-1018, at 967, 973. A clinician would therefore not expect that "getting more cyclosporin into the tissue" by increasing the amount of cyclosporin from 0.05% to 0.1% would increase therapeutic efficacy. See Dkt. No. 473, Trial Tr. 67.[35]

[35] In expressing surprise at the Phase 3 results in light of Dr. Tang-Liu's pharmacokinetic studies, Drs. Tang-Liu, Reis, and Schiffman did not account for the fact that, according to Stevenson, the formulations in the Phase 2 study showed no dose response, which indicated that increasing the amount of cyclosporin absorbed in the ocular tissue does not translate to an increase in clinical efficacy. Moreover, the Stevenson paper was available to a person of skill in

Third, the prior art made clear that increasing the amount of castor oil in the emulsion in general—and increasing the amount of castor oil in the emulsion from 0.625% to 1.25% in particular—was beneficial in the context of treating dry eye. The Ding II patent, which issued in 1999, stated that the "conventional teaching in the art [was] away from a formulation which utilizes a higher fatty acid glyceride, such as castor oil, by itself or in combination with an active agent." Ding II patent, col. 5, ll. 18-21. But the Ding II patent demonstrated that, contrary to that conventional teaching, the use of castor oil was beneficial in the vehicle emulsion used in Restasis. The Ding II patent disclosed that the emulsion provided "a high comfort level and low irritation potential suitable for the delivery of medications to sensitive areas such as ocular tissues"; in addition, the emulsion was "suitable itself for alleviating dry eye symptoms." Id., col. 3, ll. 32-38. Dr. Hanes testified that "[o]ne of ordinary skill [reading Ding II] would conclude that [the vehicle formulations] are effective in and of themselves without the cyclosporin also in treating dry eye." Dkt. No. 472, Trial Tr. 26. Even Allergan's expert Dr. Perry acknowledged that castor oil has palliative benefits for dry eye patients. Dkt. No. 475, Trial Tr. 110.

The Ding II patent showed that increasing the castor oil concentration from 0.625% to 1.25% caused an increase in the ocular residence time of the emulsion from approximately two hours to approximately two hours and 15 minutes. Ding II patent, Fig. 7. And the Ding II patent

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the art as of 2003, but Dr. Tang-Liu's internal pharmacokinetic studies were not. In determining the knowledge and expectations of a person of skill in the art at the time of the invention, as relevant to whether the results were unexpected and whether prior art publications taught away from the claimed invention, the Court must not attribute the private knowledge of the inventors to the person of skill in the art. See Bristol-Myers Squibb, 752 F.3d at 978 ("what the inventor knew at the time of the invention is irrelevant").

teaches that the "retention of the emulsion in the subject's eye is also important in achieving the objectives of the present invention." Id., col. 8, ll. 26-28.

In response to that disclosure in the Ding II patent, Allergan offered evidence that the additional period of 15 minutes residence time is not clinically meaningful, because about 90% of the cyclosporin in the emulsion is absorbed in the first five minutes, and the rest would be absorbed within the first half-hour. See Dkt. No. 475, Trial Tr. 106 (Dr. Perry). Increasing the residence time from two hours to two hours and 15 minutes would therefore not cause additional cyclosporin to be absorbed into the ocular tissue. Id.

While the increased residence time may not significantly increase the absorption of cyclosporin, it was understood in the art that the increased residence time of castor oil in the eye could nonetheless help alleviate dry eye symptoms by decreasing tear evaporation from the eye. As stated in Stevenson:

> It is important to note that the 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. One of the factors contributing to the beneficial effects of the vehicle may be its sustained residence time on the ocular surface (3 to 4 hours; data not shown). This long residence time may help reduce evaporation of the limited volume of natural tears present in patients with dry eyes.

DTX-1018, at 973. Sall says the same thing:

> As was seen in a phase 2 dose-response study [citing Stevenson], the vehicle for the [cyclosporin A] 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.

DTX-1017A, at 638; see also Dkt. No. 472, Trial Tr. 22 (Dr. Hanes: The increase in ocular residence time may contribute to the efficacy of the emulsion by "retard[ing] water evaporation from the eye which alleviates dry eye symptoms."); Dkt. No. 473, Trial Tr. 150 (Dr. Calman: Castor oil itself "has a number of beneficial effects" that are "meaningful for dry eye and KCS patients," and "there's an indication that the ocular residence time, which is a desirable characteristic, may be prolonged with the higher levels within the Ding II range."); Dkt. No. 475, Trial Tr. 69 (Dr. Perry: An emulsion with increased contact time might "make up for the decreased concentration of cyclosporin."); id. at 155 (Dr. Perry: Increasing castor oil increases residence time.).

The evaporation factor is meaningful. The parties' experts agreed that individuals experiencing dry eye symptoms may suffer from aqueous-deficient dry eye, in which not enough tears are produced, or evaporative dry eye, in which the tears evaporate too quickly from the surface of the eye, or a combination of the two. Allergan's clinical expert Dr. Perry testified that "[b]etween 50 and 70 percent" of individuals suffering from dry eye have a combination of aqueous-deficient and evaporative dry eye, Dkt. No. 475, Trial Tr. 59, and that "the presence of evaporative disease is pervasive and occurs in almost all the patients who have aqueous deficiency, and only about five to 10 percent have just pure aqueous deficiency," id. at 178. Because many patients with dry eye suffer, at least in part, from evaporative dry eye disease, a person of skill would expect that increasing the amount of castor oil, and thus increasing the residence time of the emulsion, would have beneficial effects in reducing the symptoms of dry eye.

That explanation is further supported by Allergan's theory regarding how Restasis works in general. According to Dr. Robert Noecker, in dry eye and KCS

> the surface of the eye is inflamed [and] the nerves which are basically sending the signal to make tears get suppressed because they're . . . getting irritated all the time so they kind of start to shut down. And the problem with that is then you lose your signal to make tears. And if you lose your signal to make tears, . . . then you have less tears, and then it gets more – you know, there's more friction on the surface and it gets more inflamed and there's less kind of removal of the bad stuff. And then it gets more numb and you get caught in this neural loop. . . . And the idea is to break the loop and suppress the inflammation [by delivering cyclosporin].

Dkt. No. 471, Trial Tr. 88. Restasis therefore works because it delivers cyclosporin, which suppresses ocular inflammation. Id. at 90. In that context, Restasis would provide cyclosporin to suppress inflammatory cells, but the increased residence time resulting from an increased amount of castor oil may also retard evaporation and extend the presence of tears on the eye, reducing the "friction on the surface" of the eye and the consequent inflammation. Id. at 89.

Finally, Allergan admitted years before 2003 that castor oil was beneficial in the tested emulsions. In a 1999 report on the Phase 3 trials, submitted as part of the Restasis NDA, Allergan stated that "[b]ased on the Phase-2 study results and as would be expected with a formulation designed for use in dry-eye patients, it was recognized that the vehicle, an oil emulsion formulation, probably would have some beneficial effect. The vehicle response was substantial in this study . . . ." DTX-1291A, at 96; see also id. at 98 (in the "Conclusions" section of that same report, Allergan stated that, "[a]s expected for a formulation designed for use in a dry-eye population, the vehicle delivered a significant beneficial effect to patients"). Allergan acted on that view with its decision to market a dry eye product known as Refresh Endura, which contained artificial tears together with castor oil and which was approved for sale in 2002. Dkt. No. 473, Trial Tr. 42-43, 88.

Nor is the Ding II patent the only one of Allergan's prior art patents to teach that increasing castor oil is beneficial for the treatment of dry eye. In the context of formulations

including cyclosporin, the Ding I patent discusses an experiment in which "the therapeutic level of cyclosporin was found in the [ocular] tissues of interest" not only for formulations with a cyclosporin-to-castor-oil ratio at or above 0.08, but also for a formulation with more castor oil—i.e., a cyclosporin-to-castor-oil ratio of 0.04. Ding I patent, col. 5, ll. 18-23. Those results "substantiate[] that cyclosporin in an ophthalmic delivery system is useful for treating dry eye." Id., col. 5, ll. 23-25.

Allergan's own published clinical trial information disclosed in 2000 showed that increasing castor oil in the formulation is beneficial. While the Sall paper did not explicitly disclose the amount of castor oil contained in the test formulations, the evidence showed that Sall nonetheless would have provided significant information about the castor oil content of the trial formulations. Allergan's clinical expert Dr. Perry agreed that a person of skill in the art at that time would have understood that the 0.1% and 0.05% cyclosporin formulations reported in Stevenson were the formulations disclosed in Examples 1D and 1E in Ding I. See Dkt. No. 475, Trial Tr. 147-48. A skilled artisan therefore would have been aware of the performance of the 0.05% cyclosporin/0.625% castor oil formulation as compared to the performance of the 0.1% cyclosporin/1.25% castor oil formulation in Phase 2 of the Allergan studies. See id. at 158.

Allergan argues that it is unclear from the Sall paper whether the amount of castor oil in the two cyclosporin formulations discussed in Sall was the same. Dr. Perry, who participated as a clinical investigator in Allergan's Phase 3 clinical trials, testified that he did not know the amounts of castor oil that were used in Phase 3. In fact, he stated that he "thought that the formulations in Phase 3 were the formulations that were in Phase 2." See Dkt. No. 475, Trial Tr. 96-97. Allergan's expert Dr. Loftsson testified that Sall does not tell a person of skill "whether

the formulations use the same or different amounts of castor oil" relative to the vehicle. Dkt. No. 474, Trial Tr. 91.

The Court finds the testimony of the defendants' expert Dr. Calman to be more persuasive on this point. Dr. Calman testified that having the same vehicle—and therefore the same castor oil concentrations—in Phase 3 "not only makes sense, it's appropriate science." Dkt. No. 474, Trial Tr. 24. He explained that a person of skill reading Sall would understand that "a paper like this with two identical Phase 3 trials" is "for something that's about to be submitted to the FDA because that's what the FDA requires[:] . . . two independent Phase 3 clinical trials," and "that you have a control group and that you control for all the variables except for your active ingredient." Dkt. No. 473, Trial Tr. 79; see also id. at 123 (explaining that to do a reliable study, "you need to a head-to-head study," meaning "same time, same parameters, controlling for all the other variables, same patient population, measuring the things in the same way at the same time points. It's pretty common sense, and it's the way things are done."). "[I]f, in fact, you had different vehicles in these two emulsions [in Sall], you would have to do different control groups. And the fact that there's one control group makes it clear to a person of skill in the art that they're the same. They have to be." Id. at 79.

Also persuasive was Dr. Calman's discussion of the motivation to use a control for both cyclosporin formulations. If Allergan had chosen to match the vehicle to only one of the cyclosporin formulations and not to have a control for the other, it would have run "the risk [that] the FDA would reject [its] application and say, go back and do it again, which means you lose a couple of years, you lose millions of dollars, not to mention the effort . . . this is a big piece of work. It's a big study." Dkt. No. 473, Trial Tr. 79. Dr. Reis indicated that she chose the same vehicle for both cyclosporin formulations in Phase 3, but not simply in order to avoid multiple

controls. Nonetheless, she did not testify that she would have proceeded with a control for only one of the formulations. Dkt. No. 470, Trial Tr. 80. And she confirmed that "[h]aving the oil the same across all three [both cyclosporin formulations and the vehicle] seemed desirable." Id. at 80-81.

Dr. Reis testified that it was "unusual" to "change the formulation between Phase 2 and Phase 3 clinical studies," and that "clinical people don't like to do [that] because you feel like you're flying a bit blind." Dkt. No. 473, Trial Tr. 81. However, the Court does not find that the atypical change from Phase 2 to Phase 3 would have prompted Allergan to go against common practice (and FDA requirements) by not using a consistent control.

Dr. Calman's position is reinforced by the Sall paper itself. Sall states that "[t]wo identical, multicenter, randomized, double-masked, parallel-group clinical trials were conducted to compare two concentrations of [cyclosporin A] emulsions to its vehicle." DTX-1017A, at 632. The phrase "its vehicle" is singular, and it refers to both cyclosporin formulations. The implication from the text of Sall is that each formulation used the same vehicle, containing the same amount of castor oil. Compare DTX-1018, at 968 (Stevenson: In the flexible Phase 2 study, which was designed for dose-ranging purposes and not necessarily for accurate statistical significance, "[t]he vehicle for each concentration of cyclosporin A ophthalmic emulsion [was] formulated slightly differently because greater oil content is required to dissolve the higher concentrations of the active ingredient," and the vehicle for the 0.2% cyclosporin formulation "was chosen for the control because it was near the middle of the range of cyclosporin A concentrations used.").

Based on the premise that the vehicle in each of the Phase 3 formulations discussed in Sall contained the same amount of castor oil, a person of skill would understand that the amount

of castor oil in the 0.05% formulation had to be greater than 0.625%. That is because Ding I made clear that the ratio of cyclosporin to castor oil should preferably be between 0.02 and 0.12 in order to dissolve all of the cyclosporin and maintain the stability and shelf life of the emulsion. Dkt. No. 469, Trial Tr. 162-63 (testimony of Allergan formulator); see also Ding I, col. 3, ll. 17-20. Therefore, it was necessary for the vehicle to contain more than 0.83% castor oil (the ratio of 0.1% cyclosporin to 0.833% castor oil is 0.12).[36] That means that the amount of castor oil in the 0.05% formulation (originally 0.625) must have been increased. Thus, even assuming, with Allergan, that Stevenson and Sall show that Restasis performed better than the 0.05% formulation of Phase 2 and at least as well as the 0.1% formulation of Phase 3, Sall shows that those improved clinical outcomes resulted from increasing the concentration of castor oil in the 0.05% cyclosporin formulation from 0.625% to at least 0.83%. A person of skill would therefore have appreciated from Sall (and would not have found it surprising) that increasing the amount of castor oil in the 0.05% formulation would provide an improvement in performance over the 0.05% formulation of Phase 2, or at least would not result in a decrease in efficacy.

Allergan emphasizes that the chemical arts in general, and the field of ophthalmic formulations in particular, are unpredictable. In response to counsel's question at trial as to whether "formulating in the ophthalmic arts is – are the results pretty predictable or unpredictable," Allergan formulator Dr. Olejnik testified that the results are "[u]npredictable" in his experience. Dkt. No. 469, Trial Tr. 141. That may be so, but any unpredictability in the field of ophthalmic formulations does not change the fact that in this instance the prior art was replete

[36] Allergan's expert Dr. Perry confirmed that the amount of castor oil used in the 0.05% cyclosporin formulation had to be at least 0.833% in order to satisfy the preferred ratio of cyclosporin to castor oil disclosed in Ding I. Dkt. No. 475, Trial Tr. 80-81.

with information, much of it from Allergan itself, as to the predictable efficacy of the cyclosporin/castor oil formulation that ultimately became Restasis.

While it is true that the prior art did not explicitly disclose the formulation for Restasis (although the Ding I patent came close), proof of unexpected results requires more than a modest deviation from what was disclosed in the prior art. As previously noted, unexpected results are probative of nonobviousness only if they are "different in kind and not merely in degree from the results of the prior art." In re Huang, 100 F.3d at 139. It has long been held that routine optimization within a previously disclosed range of values does not give rise to a patentable invention, absent a showing of unexpected and surprising results. See In re Applied Materials, Inc., 692 F.3d 1289, 1295 (Fed. Cir. 2012); In re Peterson, 315 F.3d at 1330 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of . . . ranges is the optimum combination."); In re Boesch, 617 F.2d 272, 276 (C.C.P.A. 1980) (showing of obviousness may be rebutted "where the results of optimizing a variable, which was known to be result effective [are] unexpectedly good") (quoting In re Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977)); In re Aller, 220 F.2d at 456 ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). When differences based upon degree are asserted, the evidence must show "that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected." In re Merck & Co., 800 F.3d 1091, 1099 (Fed. Cir. 1986).

In this case, the Ding I patent disclosed a 0.05% cyclosporin formulation with 0.625% castor oil and a 0.1% cyclosporin formulation with 1.25% castor oil. All other components of the formulation were the same as in the Restasis patents. The Sall paper, moreover, showed that

a 0.05% cyclosporin formulation could be effective in treating dry eye and KCS, even though Sall did not disclose the amount of castor oil in the formulation. In order to avoid a finding of obviousness, it would have taken a showing that the particular combination of 0.05% cyclosporin and 1.25% castor oil produced exceptional results different in kind from those that would have been expected based on the Ding patents and the Sall paper. The Court finds that the evidence in this case shows no such exceptional results for the formulation that became Restasis. In addition, and for the same reasons, the Court finds that the prior art did not teach away from the use of a 0.05% cyclosporin/1.25% castor oil emulsion as a potentially effective treatment for dry eye and KCS.

B. Objective Indicia (or Secondary Considerations)

Allergan places considerable weight on its evidence of objective indicia of nonobviousness. It relies particularly on the commercial success of Restasis and the long-felt unmet need for a pharmaceutical that would provide effective treatment—and not just palliative relief—for dry eye and KCS, without significant side effects. Those factors, according to Allergan, weigh in favor of a finding that the asserted claims would not have been obvious as of the 2003 priority date of the Restasis patents.[37]

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[37] Allergan characterizes "unexpected results" as a secondary consideration. In the Court's view, however, in a case such as this one that factor is more appropriately viewed not as a secondary consideration, but as part of the initial stage of the obviousness analysis. For that reason, the Court has analyzed the unexpected results argument in part I.A., rather than as one of the objective considerations discussed in part I.B. But regardless of how the issue is categorized as a doctrinal matter, the analysis is the same. After close analysis of the "unexpected results" issue, above, the Court has found that the supposedly unexpected results do not justify a conclusion that the Restasis patents would not have been obvious. To be clear, however, regardless of how the unexpected results issue is characterized, the Court has considered the evidence on that issue, as well as the evidence of the (other) objective indicia of nonobviousness, together with all of the other evidence pertaining to the obviousness inquiry, as the Federal

It is well settled that objective indicia—sometimes referred to as "secondary considerations"—must be taken into account in any obviousness analysis, and that such evidence can support a finding of nonobviousness. WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016); Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1349 (Fed. Cir. 2012). In fact, as the Federal Circuit has said, "evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." Apple Inc. v. Samsung Elecs. Co., 839 F.3d 1034, 1052-53 (Fed. Cir. 2016) (en banc) (quoting Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39 (Fed. Cir. 1983)). However, "[f]or objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the *claimed invention*." In re Huai-Hung Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quoting Wyers v. Mater Lock Co., 616 F.3d 1231, 1246 (Fed. Cir. 2010)).

There is no doubt that Restasis has been a commercial success. The existence of this lawsuit is practically res ipsa loquitur in that regard, as it is unlikely that the parties would have invested the substantial resources consumed by this litigation if the product in dispute were not successful. Moreover, Allergan introduced evidence that Restasis has generated very large sales and considerable profits. In the year 2015, for example, Restasis had net sales of $1.2 billion on which the company generated a pre-tax profit of approximately $975 million. Dkt. No. 474, at 159-61. And one of the defendants' own representatives admitted that he regarded Restasis as a

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Circuit has instructed. See, e.g., Intercontinental Great Brands LLC v. Kellogg N. Am. Co., No. 2015-2082 (Fed. Cir. Sept. 7, 2017), slip op. 16-17 (citing cases).

successful product. Dkt. No. 471, Trial Tr. 38-39. The defendants do not seriously challenge Allergan's showing on the commercial success issue.

The Court also finds that Restasis satisfied a long-felt but unmet need, although the evidence on that issue is not quite as compelling as the evidence of commercial success. The existence of a long-felt need for a particular product, or for the solution to a particular problem, is well recognized as a factor supporting a finding of nonobviousness. In re Cyclobenzaprine, 676 F.3d at 1082-83.

To be sure, as the defendants have shown, there were treatments for dry eye before Restasis, and Restasis is effective for only a subset of all patients who suffer from dry eye. Restasis therefore is not a panacea. Nonetheless, witnesses for both sides testified that Restasis works very well for approximately 15 percent of all dry eye patients and has some beneficial effects for a larger percentage of patients. Dkt. No. 469, Trial Tr. 66; Dkt. No. 473, Trial Tr. 58-59; Dkt. No. 474, Trial Tr. 47.

Importantly, prior to Restasis there were no treatments for dry eye and KCS that would restore patients' natural tearing without significant risk of adverse side effects. The most common treatment for dry eye before Restasis (and since) has been the use of artificial tear eye drops. Treatment with artificial tears can offer short-term relief for dry eye symptoms, especially in cases of mild-to-moderate severity, but artificial tears do not increase the natural production of tears or address the inflammation that is typically associated with dry eye, so the relief is temporary and merely palliative in nature. See Dkt. No. 469, Trial Tr. 29-30; Dkt. No. 471, Trial Tr. 91; Dkt. No. 473, Trial Tr. 42-43; Dkt. No. 475, Trial Tr. 114-15.

The use of corticosteroids can be effective in treating dry eye and reducing the associated inflammation. Corticosteroid use, however, has generally been limited to short-term treatment

because, as previously noted, long-term use of corticosteroids in the eye can cause cataracts or an increase in intra-ocular pressure that is associated with glaucoma. Dkt. No. 469, Trial Tr. 31; Dkt. No. 473, Trial Tr. 57; Dkt. No. 475, Trial Tr. 60-61. As a result, any long-term use of corticosteroids must be monitored closely and discontinued if the patient develops any potentially serious side effects.

Another form of treatment occasionally used to treat dry eye is the surgical insertion of punctal plugs to block the drainage of tears from the eye and thus retain natural tears on the ocular surface for a longer period of time. See Dkt. No. 469, Trial Tr. 30. That approach, however, has the undesirable consequence of allowing inflamed tears to remain in the eye for longer periods of time, which can exacerbate the condition for some patients. Id.

More recently, in 2016, a product known as Xiidra was approved to treat the signs and symptoms of dry eye disease, Dkt. No. 474, Trial Tr. 191-92; Dkt. No. 475, Trial Tr. 20-21, but that product was not on the market at the time Restasis was invented, so it is not relevant to the presence of a long-felt need as of the priority date for the Restasis patents. Thus, the evidence shows that, for at least some patients, Restasis has met a long-felt need that was not adequately addressed by prior art medicines and procedures.

The problem with Allergan's evidence of both commercial success and long-felt need is that Allergan's patents have long blocked others from entering the space in the market that is now occupied by Restasis. Allergan has enjoyed patent protection for the topical administration of cyclosporin to the eye since obtaining rights under the Kaswan patent in 1993. The Ding I patent issued shortly thereafter in 1995 and expired in 2014. The Ding I patent conferred patent protection on Allergan for emulsions containing cyclosporin and higher fatty acid glycerides,

including castor oil. Just before the Ding I patent expired, Allergan obtained the Restasis patents in late 2013 and early 2014.

As the Federal Circuit has explained, commercial success is relevant "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." Merck & Co. v. Teva Pharm. USA, Inc., 395 F.3d 1364, 1376 (Fed. Cir. 2005). However, where market entry by others was precluded due to blocking patents, the inference of non-obviousness from evidence of commercial success is weak. Id. at 1377; Galderma, 737 F.3d at 740; Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371, 1383 (Fed. Cir. 2005); Sanofi-Sythelabo v. Apotex Inc., 488 F. Supp. 2d 317, 337-38 (S.D.N.Y. 2006). This is such a case.

In Galderma, another case involving a pharmaceutical composition, the patentee had patent rights that blocked the market entry of the composition at issue until long after the patentee invented the claimed composition. As such, the Federal Circuit explained, the patentee could not have successfully brought the composition to market before the previous patents expired. Accordingly, the court concluded that the commercial success factor was of "minimal probative value." 737 F.3d at 740-41.

As in Galderma, the patent protection provided by the Kaswan and Ding I patents barred any competition in the field of cyclosporin-based emulsions with higher fatty acid glycerides, including castor oil, even though the benefits of castor oil and the combination of castor oil and cyclosporin in treating dry eye were known well before the priority date of the Restasis patents. From the evidence before it, the Court finds that while Restasis has been a commercial success, that success is attributable mainly to the patent protection Allergan has enjoyed for cyclosporin/castor oil emulsions over the past quarter century.

The same analysis applies to the objective consideration of long-felt but unmet need. While there was ample incentive to invent an appropriate ophthalmic product that would have anti-inflammatory properties, the option to invent in the area of castor oil/cyclosporin emulsions was closed to those outside of Allergan. Thus, it was Allergan that met that need, not because Allergan was at the forefront of innovation in a competitive setting, but because it had enjoyed a long period of patent protection, which ensured that it would be the only party that would be able to invent and exploit a cyclosporin/castor oil product.

Through Dr. Perry, Allergan submitted evidence at trial as to the failure of others, a factor that sometimes serves as an objective consideration bearing on obviousness. See In re Cyclobenzaprine, 676 F.3d at 1081-82. The evidence on that issue, however, was quite spare. Except for a brief description of Sandoz's unsuccessful effort to develop a treatment consisting of cyclosporin in corn oil (which failed because it was not well tolerated by patients), Dkt. No. 475, Trial Tr. 115-16, Dr. Perry's testimony on the subject was limited to a brief listing of companies that had unsuccessfully attempted to develop treatments for dry eye disease, id. at 116-17. He testified that two companies had unsuccessfully tried to develop a cyclosporin-based treatment for dry eye disease involving formulations having concentrations of 0.1% and 0.2% cyclosporin. Id. at 116. He then listed three other drugs that had been studied as possible non-cyclosporin-based treatments for dry eye but had been unsuccessful or had not been approved by the FDA. Id. at 116-17.

That evidence is of limited relevance, because Dr. Perry's brief listing of the other efforts to devise treatments for dry eye sheds no light on whether their failures were based on the nonobviousness of the Restasis patents or on other reasons. Nor did Dr. Perry identify when those efforts were made. The prior art in this case indicated that as of the 2003 priority date for

the Restasis patents it was known that cyclosporin/castor oil formulations—and in particular formulations containing 0.1% cyclosporin or 0.05% cyclosporin—were both safe and effective in treating dry eye. For that reason, proof of the failure of others would be irrelevant unless it showed that others were unable to develop a cyclosporin/castor oil formulation similar to Restasis despite having the Ding I patent, the Ding II patent, and the Sall paper to consult. Nothing in Dr. Perry's evidence of the failure of others suggests that. Instead, the best explanation for the failure of others to develop an effective cyclosporin/castor oil treatment after 2000 in light of the prior art at that time is that the rights to that formulation were owned by Allergan through the Ding I patent.

Finally, Allergan briefly asserts that the evidence of the defendants' copying of Restasis is indicative of nonobviousness. But there are strong incentives in the Hatch-Waxman process for generic drug companies to copy FDA-approved drugs, as the statute allows them to avoid the lengthy and expensive approval process if they can show that their products are bioequivalent to the brand name drug. For that reason, the Federal Circuit has explained that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013); see also Purdue Pharma Prods. L.P. v. Par Pharm., Inc., 377 F. App'x 978, 983 (Fed. Cir. 2010). The fact that the defendants have copied the Restasis formulation in order to facilitate their showing of bioequivalence for purposes of obtaining FDA approval of their ANDAs is therefore not probative of nonobviousness.

In sum, based principally on the presence of the blocking patents that suppressed any competition in cyclosporin/glyceride emulsion formulations, the Court concludes that the objective consideration evidence does not significantly support a finding of non-obviousness.

C. Other Limitations

In its proposed findings of fact and conclusions of law, Allergan does not suggest that any of the other limitations of the asserted claims avoid a conclusion of obviousness. Nor was there any dispute at trial regarding those additional limitations. Nonetheless, for completeness, the Court will briefly review each of the limitations of the asserted claims and where they are found in the prior art.

The components of the claimed formulation are essentially the same in all of the asserted claims of the composition and method claims. Those components, other than the percentages of cyclosporin and castor oil in the 0.05% cyclosporin formulation, discussed above, are set forth in Ding I. See Ding I patent, col. 4, ll. 31-62; id., col. 6, ll. 27-41. The limitation requiring that cyclosporin A be the only peptide present in the topical ophthalmic emulsion, which is found in claims 26 and 27 of the '111 patent (through independent claim 21), is disclosed in the Ding I patent, which claims a pharmaceutical emulsion "consisting of" components including only one peptide, cyclosporin. Id., col. 6, ll. 35-41; Dkt. No. 472, Trial Tr. 34. The requirements that the emulsion be therapeutically effective in treating KCS and increasing or restoring production are found in claims 26 and 27 of the '111 patent, in claim 35 of the '930 patent (through independent claim 25), and in all the asserted claims of the '048 and '191 patents. Both of those limitations are shown in Sall, DTX-1017A, at 637, and in the Ding I patent, col. 1, ll. 10-16; id., col. 5, ll. 10-25. The requirement that the blood of the person being treated contain substantially no detectable concentration of cyclosporin, which is found in claim 35 of the '930 patent, claim 11

of the ’048 patent, and claims 13, 16, 22, and 27 of the ’191 patent, is also shown in Sall.[38] DTX-1017A, at 637.

As for the additional limitations in the asserted method claims of the ’048 and ’191 patents, the twice-a-day dosage frequency, which is found in all of the asserted claims of those patents, is disclosed in Sall. DTX-1017A, at 632, 637. The requirement that the claimed emulsion be “as substantially therapeutically effective as a second emulsion . . . comprising cyclosporin A in an amount of 0.1% by weight and castor oil in an amount of 1.25% by weight,” which is found in claims 13 and 14 of the ’048 patent and claims 13, 16, and 22 of the ’191 patent, is also disclosed in Sall. Id. at 634-37. The requirement that the method be effective in enhancing lacrimal gland tearing, found in claims 16 and 26 of the ’191 patent, is shown in Sall. Id. at 637. The requirement that there be a reduction in adverse events compared to a 0.1% cyclosporin emulsion, found in claim 22 of the ’191 patent, and the requirement that the adverse events be either visual distortion or eye irritation, found in claim 27 of the ’191 patent, are both disclosed in the Sall paper. Id. at 636. And, finally, the requirement that the emulsion have a pH in the range of about 7.2 to 7.6, found in claim 23 of the ’191 patent, is disclosed in the Ding I patent, col. 4, line 31, through col. 5, line 9.

Allergan has not suggested that there is no motivation to combine the prior art references for purposes of the obviousness analysis. Because the Ding I patent is plainly related to both the Ding II patent and (as Allergan’s own expert admitted, Dkt. No. 475, Trial Tr. 147-48) the formulations tested in Phase 2 and Phase 3 were reported in Sall, the Court finds that there was a

[38] Claims 22 and 27 of the ’191 patent specify that the concentration of cyclosporin in the blood of the human must be less than one nanogram per milliliter. That limitation is also disclosed in the Sall paper. DTX-1017A, at 637.

clear motivation to combine the prior art references (all owned or sponsored by Allergan). A person of skill in the art would have regarded them as being essentially a single set of closely related references. The Court further finds that a skilled artisan would have had a reasonable expectation of success regarding the Restasis formulation based on the Ding I patent, which discloses an example with 0.05% cyclosporin (Example 1E), confirms that a cyclosporin-to-castor-oil ratio of 0.04 falls within a preferred range, and claims compositions with an amount of castor oil between about 0.625% and about 5.0%. The Sall and Ding II references confirm that expectation of success.

In view of all the evidence, including the prior art, the evidence of unexpected results, the evidence of objective considerations, and the motivation to combine the prior art references of Sall and the Ding I and Ding II patents, the Court concludes that the defendants have satisfied their burden of showing by clear and convincing evidence that the asserted claims of the Restasis patents would have been obvious.[39]

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[39] The defendants argue that the asserted claims are invalid due to obviousness-type double patenting in light of the Ding I patent, but it is not clear to the Court what additional benefit the defendants believe they obtain from their double-patenting argument that is not available to them under their obviousness argument.

Obviousness-type double patenting is a court-made rule that prohibits an applicant from effectively extending the term of a patent by obtaining a claim in a second patent that is merely an obvious variation of a claim the applicant obtained in an earlier patent. Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc., 592 F.3d 1340, 1346 (Fed. Cir. 2010). In order to survive a double patenting challenge, the claims of the later patent must be patentably distinct from the claims of the earlier one, i.e., the later claims must not be obvious over earlier claims by the same inventor. See AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1373 (Fed. Cir. 2014). The doctrine of obviousness-type double patenting was developed to deal with the situation in which neither of two patents is citable as prior art to the other, typically because they have the same priority date. See Eli Lilly & Co. v. Barr Labs., 251 F.3d 955, 967 (Fed. Cir. 2001); id. at 973 (Newman, J., dissenting). In that setting, the court must make an obviousness determination based on the claims of the first patent, but without considering the disclosure in the specification of that patent (except to the extent necessary to

II. Invalidity Based on Anticipation

The defendants next argue that all of the asserted claims of the Restasis patents are anticipated by the Ding I patent. That argument is meritless.

It is well settled that in order to anticipate a patent claim, a single prior art reference must contain all of the limitations of the asserted claim, either explicitly or inherently. See In re Omeprazole Patent Litig., 483 F.3d 1364, 1378 (Fed. Cir. 2007). For inherent anticipation, the missing descriptive materials must be necessarily present in the prior art, not merely probably or possibly present. See Trintec Indus., Inc. v. Top-U.S.A. Corp., 295 F.3d 1292, 1295 (Fed. Cir. 2002); Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). That exacting standard was not met here with regard to the Ding I patent.

To begin with, a number of the asserted claims contain a limitation requiring twice-a-day dosing. That limitation is found in all the asserted claims of the '048 patent (claims 1, 11, 13, 14, and 23), and in all the asserted claims of the '191 patent (claims 13, 16, 22, 26, and 27). The defendants conceded at trial that the Ding I patent does not disclose twice-a-day dosing. Dkt. No. 474, Trial Tr. 70-71; Dkt. No. 476, Trial Tr. 15. By the defendants' own admission, then, those claims are not anticipated.

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construe the claims). See Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1378-79 (Fed. Cir. 2012); General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1281 (Fed. Cir. 1992).

It would make no sense in a case such as this one to consider the claims of the Ding I patent but not the specification of the Ding I patent, since both the claims and the specification of that patent are clearly in the prior art. In any event, on the facts of this case the rules that apply to double patenting would not provide any benefit to the defendants that is not already provided by the law of obviousness. Thus, in the circumstances of this case, the obviousness-type double patenting claim folds into the obviousness claim and adds nothing to it. The Court will therefore not separately address the issue of double patenting in this case.

The remaining three claims (claims 26 and 27 of the '111 patent and claim 35 of the '930 patent) are the only claims as to which the anticipation argument survives the defendants' concession. The problem with the defendants' anticipation argument regarding those three claims is that the Ding I patent does not disclose the precise percentages of cyclosporin and castor oil that are found in Restasis.

The Federal Circuit has made clear that a generic disclosure does not necessarily anticipate every species within the genus. See Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1083-84 (Fed. Cir. 2008); Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006); Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash., 334 F.3d 1264, 1270 (Fed. Cir. 2003). To the contrary, a generic disclosure in a prior art reference is held to anticipate an incorporated species only where the generic disclosure identifies the claimed species with "sufficient specificity," where the prior art reference expresses "specific preferences" for one or more particular species, or where the genus disclosed in the prior art reference is sufficiently small that the disclosure of the genus effectively describes the species. See AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Tr., 764 F.3d 1366, 1379 (Fed. Cir. 2014); Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1380 (Fed. Cir. 2001); Atofina, 441 F.3d at 999; In re Petering, 301 F.2d 676, 682-83 (C.C.P.A. 1976). That question is a factual issue that depends on the specificity of the disclosure in the prior art reference. The standard for finding that a prior art genus anticipates an incorporated species is significantly more restrictive than the standard for determining whether a prior art genus renders obvious a species that is incorporated within it. See Sanofi-Synthelabo, 550 F.3d at 1084.

In this case, the Ding I patent disclosed a genus—all formulations having concentrations of cyclosporin and castor oil falling within the claimed ranges, along with the other components

of the claimed emulsions. Ding I also disclosed several particular species within that genus—the formulations found in Examples 1A through 1E of that patent. However, the specific embodiments disclosed in Ding I do not anticipate the Restasis patent formulation claims, because none of the formulations set forth in Examples 1A through 1E of Ding I is Restasis and because there is nothing in Ding I that points specifically to the particular combination of component values in Restasis.

In arguing to the contrary, the defendants rely heavily on the testimony of their expert Dr. Hanes, who stated that in his opinion the examples set forth in Ding I effectively disclose the Restasis formulation. He based that opinion in substantial part on his view that the two ratios of cyclosporin to castor oil that were disclosed and tested in Example 1 of the Ding I patent (ratios of 0.04 and 0.08) were the "most preferred" embodiments of Ding I. Dkt. No. 472, Trial Tr. 47-48; see also Dkt. No. 471, Trial Tr. 189. From that premise, Dr. Hanes concluded that the two formulations that would "jump out" would be to change Examples 1D and 1E of Ding by doubling the amount of castor oil, thus producing the other one of the two "most preferred" ratios of cyclosporin to castor oil: 0.04. Dkt. No.471, Trial Tr. 190. One of the two formulations resulting from doubling the amount of castor oil in Examples 1D and 1E would be the formulation for Restasis.

The flaw in Dr. Hanes's analysis is his conclusion that the Ding I patent regarded 0.04 and 0.08 as the "most preferred" ratios of cyclosporin to castor oil. While it is true that the tested embodiments in Example 1 contained those ratios, there was no indication that those ratios were particularly preferred, as opposed to simply being intermediate points in the preferred ratio range of 0.02 to 0.12 that would be suitable for testing. After the "most preferred" label for the 0.04 and 0.08 ratios is removed, it is evident that the number of possible formulations satisfying the

parameters set forth in Ding I is much larger than the two identified by Dr. Hanes. Thus, the Court concludes that the Ding I patent does not express a "specific preference" for the Restasis species, and the number of candidate species within the genus described in Ding I is not so small that the description of the genus effectively describes the species.

The Court therefore finds that the prior art does not describe the Restasis formulation with sufficient specificity to satisfy the test for anticipation.

III. Invalidity for Improper Inventorship

The defendants argue that the Restasis patents are invalid under 35 U.S.C. § 102(f) (2006), because the inventors named on the patents were not the true inventors of the patented inventions.[40] That provision states that "[a] person shall be entitled to a patent unless . . . he did not himself invent the subject matter sought to be patented." If the list of named inventors on a patent is incomplete, i.e., some true inventors are not named (a condition known as nonjoinder), or if the list of named inventors is overinclusive, i.e., some of the named inventors are not true inventors (a condition known as misjoinder), then the patent is subject to invalidation unless it is corrected. See Pannu v. Iolab Corp., 155 F.3d 1344, 1350 (Fed. Cir. 1998).

"There is a 'presumption that [a patent's] named inventors are the true and only inventors.'" Drone Techs., Inc. v. Parrot S.A., 838 F.3d 1283, 1292 (Fed. Cir. 2016) (quoting Alps S., LLC v. Ohio Willow Wood Co., 787 F.3d 1379, 1382 (Fed. Cir. 2015)); see also

[40] Under the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 286 (2011), section 102(f) was eliminated. Inventorship requirements under the AIA now appear in 35 U.S.C. § 115(a). Id., 125 Stat. 293-94. This case is governed by the pre-existing section 102(f), because the pre-AIA version of that provision governs cases (such as this one) involving patents with an effective filing date before March 16, 2013. The same effective date applies to other AIA provisions applicable to this case, so the pre-AIA version of the Patent Act applies throughout.

Cumberland Pharms. Inc. v. Mylan Institutional LLC, 846 F.3d 1213, 1218 (Fed. Cir. 2017). "[A] party alleging misjoinder or non-joinder of inventors must meet the heavy burden of proving its case by clear and convincing evidence." Eli Lilly & Co. v. Aradigm Corp., 376 F.3d 1352, 1358 (Fed. Cir. 2004); see also Cumberland, 846 F.3d at 1218; Pannu, 155 F.3d at 1349; Hess v. Advanced Cardiovascular Sys., Inc., 106 F.3d 976, 980 (Fed. Cir. 1997). Parties other than an alleged inventor may bring claims of incorrect inventorship under section 102(f) to challenge the validity of the patent. See, e.g., Pannu, 155 F.3d at 1348 (alleged infringer may raise invalidity defense based on nonjoinder of third-party inventor under section 102(f)); Schulze v. Green, 136 F.3d 786, 788, 792 (Fed. Cir. 1998) (non-inventor may challenge patent validity under section 102(f) based on misjoinder).

Prior to trial, the defendants did not raise the issue of misjoinder, i.e., they did not contend that any of the four named inventors should not have been named as inventors on the Restasis patents. Nor did they claim that Dr. Reis should have been named as an inventor on the Restasis patents. Instead, the defendants' inventorship claim was limited to asserting that Dr. Ding, who was not named on the patents, should have been named as an inventor. In particular, in their lengthy invalidity contentions, amended on several occasions, the defendants focused their inventorship allegations entirely on the failure to name Dr. Ding as an inventor on the Restasis patents; they did not raise a claim of misjoinder or contend that Dr. Reis should have been named as an inventor. See Dkt. No. 303-1, at 213-19. In their proposed findings of fact and conclusions of law, however, the defendants now assert that the Restasis patents are invalid "for naming the wrong inventive entity, including the failure to name Dr. Ding and/or Dr. Reis as inventor(s)." Defendants' Post-Trial Proposed Findings of Fact, Dkt. No. 492, ¶ 332, at 97. In addition, the defendants now contend that "[n]one of the inventors currently named on the

patents-in-suit conceived of what Allergan characterizes as the invention claimed in the patents-in-suit: formulating 0.05% cyclosporin in a vehicle that contains 1.25% castor oil." Id. ¶ 319, at 95.

The Court rejects the defendants' effort to broaden the scope of their inventorship argument to include a claim of misjoinder of the four named inventors, Dr. Acheampong, Dr. Tang-Liu, Dr. James N. Chang, and Mr. David F. Power, as well as an argument of non-joinder as to Dr. Reis. Because those theories of invalidity based on improper inventorship were not raised in the defendants' invalidity contentions, they have been waived. For that reason, the Court will address the defendants' claim that Dr. Ding should have been joined as an inventor of the Restasis patents, but will not address the question whether the patents are invalid because some or all of the named inventors should not have been included on the patents, or because Dr. Reis should have been named as an inventor.[41]

Although Dr. Ding was a named inventor in the Ding I and Ding II patents, the evidence was unclear as to whether she should have been named as an inventor on the Restasis patents. While two of the named inventors, Dr. Chang and Mr. Power, offered their opinions that Dr. Ding was an inventor of the Restasis formulation, both of them qualified their opinions in that regard by acknowledging their lack of direct knowledge regarding her contributions to the project. Moreover, and more importantly, Dr. Ding's own testimony tended to show that she was not an inventor of the Restasis formulation.

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[41] The defendants' current position that Dr. Ding should have been named as an inventor is in tension with their position at trial, where they argued that the evidence showed that Dr. Ding was not an inventor. Dkt. No. 471, Trial Tr. 157-59. Rather, their position at trial was that the evidence had not identified anyone who qualified as an inventor, including Dr. Ding. Id. at 158-59.

The evidence showed that, as a formulator, Dr. Ding was significantly involved in the Restasis project. She testified about her involvement in creating the formulations that were used in the Ding I and Ding II patents, on which she was the lead named inventor. Dkt. No. 470, Trial Tr. 50-53. However, when asked "did you come up with" the formulation found in Composition II of Example 1 in the Restasis patents (the formulation that ultimately became Restasis), she testified, "I didn't come up with that." Id. at 53. She stated that she "was involved in the formulation[s]" that were used in the Phase 3 studies and gave those formulations to the project team. Id. at 56. But she then explained that "whatever we move forward to clinical is whatever the team desired would be most reasonable with highest chance of success. But it's not determined by – it's not decided by formulator, so it's a team scope." Id. at 57. In response to the question whether she proposed the two formulations for the Phase 3 clinical studies, she responded, "It was not formulator. Put it this way, remember Phase 2 is [dose] ranging. So they are a range of dose tested in human already. Clinical – clinical division will decide which concentration they want to study in Phase 3. It's not a formulator's call. . . . It's not my recommendation. So I really wasn't involved in this way. From Phase 2 to Phase 3, it's really clinical decide which concentration will move." Id. She added that she provided the formulations and vehicles "ordered by clinical division. . . . We are just responsible for making." Id. Because the evidence of inventorship is inconclusive, the Court relies on the presumption of correct inventorship to hold that it was not improper for Dr. Ding to have been omitted as a named inventor.

If the evidence on inventorship makes anything clear, it is that the invention of the Restasis formulation cannot easily be attributed to a single individual or a discrete set of individuals. As the evidence at trial indicated, the invention of Restasis was a collaborative

effort by a number of individuals, including those on the "cyclosporin team" at Allergan, a situation that is not unusual in a large research facility. Dkt. No. 470, Trial Tr. 470-71; see also Richard C. Witte & Eric W. Guttag, Employee Inventions, 71 J. Pat. & Trademark Office Soc'y 467, 476 (1989) ("Most employee inventions which occur in corporate R&D departments are usually the result of the collaborative efforts of several persons, rather than one individual."). In addition, the "invention" in this case was the product of clinical testing results that the test designers, according to their testimony, did not expect. There was no conception of the invention prior to the analysis of the experimental results. See Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1992) ("In some instances, an inventor is unable to establish a conception until he has reduced the invention to practice through a successful experiment."). Nor was there any "Eureka!" moment in this case by a single inventor or set of inventors working together, but rather a collective recognition that, contrary to what members of the Allergan cyclosporin team said they expected, the 0.05% cyclosporin formulation did well in the Phase 3 studies and would make a suitable drug.

The statute governing the naming of inventors, 35 U.S.C. § 116 (2006), was amended in 1984 to deal with situations such as the one in this case. As amended, section 116(a) provides, inter alia, that inventors may apply for a patent jointly even if they did not work together physically or at the same time, and even if each did not make the same type or amount of contribution. See generally Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1469-70 (Fed. Cir. 1998) (Newman, J., dissenting). In a case in which it is difficult to pinpoint a single individual or set of individuals who conceived of the invention and then reduced it to practice, it is appropriate to invoke the presumption of correct inventorship, thus respecting the decision of the collaborators on the research project to resolve among themselves the credit for an invention

that may have been more collectively stumbled upon than individually devised. The Court therefore holds that it was not improper to omit Dr. Ding from inclusion in the group of named inventors. For that reason, the defendants' request to invalidate the Restasis patents for improper inventorship is denied.[42]

IV. Invalidity Based on Lack of Enablement

The defendants next contend that the Restasis patents do not satisfy the enablement requirement of section 112 of the Patent Act, 35 U.S.C. § 112, ¶ 1 (2006). The defendants' enablement argument focuses on the claim term "acrylate/C10-30 alkyl acrylate cross-polymer," which is the emulsion stabilizer component of the formulation recited in each of the asserted claims. See, e.g., '111 patent, col. 11, ll. 29-38; Dkt. No. 472, Trial Tr. 53-54, 63.

The parties did not identify the term "acrylate/C10-30 alkyl acrylate cross-polymer" as a term needing construction, either during the claim construction proceedings or on summary

[42] In an earlier motion for summary judgment, the defendants sought dismissal for lack of standing, based on their inventorship argument. Dkt. No. 338. That motion was denied. Dkt. No. 392. The Court ruled at that time that even if the defendants were correct that Dr. Ding should have been included as an inventor, Allergan would have both prudential standing and Article III standing in this action, because the evidence showed that each of the Allergan employees, including Dr. Ding, executed employment agreements that assigned to Allergan all of their rights to any inventions for which they were responsible during their tenure at Allergan. The Court reaches the same conclusion with respect to Dr. Reis, who executed a similar employment agreement assigning her rights to any intellectual property rights that inured to her in the course of her employment with Allergan. See Dkt. No. 747, Trial Tr. 175-78; PTX-333; PTX-1021. Through those agreements, Allergan thus owned all of the rights to the Restasis patents, regardless of which Allergan employees are regarded as the proper inventors. At trial, the defendants provided very little evidence, much less clear and convincing evidence, that none of the four named inventors were actually inventors and that Allergan therefore lacks standing. See, e.g., Dkt. No. 470, Trial Tr. 171 (named inventor Dr. Acheampong: "[N]o one person . . . came up with the formulation. It was a team effort" that included him.).

judgment. It has become evident, however, that it is necessary to construe that term before reaching the issue of enablement.

The discussion of the cross-polymer component is confined mainly to a single paragraph in the common specification of the Restasis patents, which reads as follows:

> One particularly useful emulsion stabilizing component includes crosslinked polyacrylates, such as carbomers and Pemulen® materials. Pemulen® is a registered trademark of B.F. Goodrich for polymeric emulsifiers and are commercially available from B.F. Goodrich Company, Specialty Polymers & Chemicals Division, Cleveland, Ohio. Pemulen® materials include acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol.

'111 patent, col. 11, ll. 29-38.[43]

Although the specification referred to specific examples of the cross-polymer emulsion stabilizers, including Pemulen materials and carbomers, the original claims in the Restasis patent applications claimed only "Pemulen" as the emulsion-stabilizing component. See PTX-2D, at 2 (claims 37, 44, 54, 60). The examiner rejected those claims as indefinite under 35 U.S.C. § 112, ¶ 2 (2006). The problem, according to the examiner, lay in the use of "the trademark/trade name Pemulen." A trademark or trade name "cannot be used properly to identify any particular material or product," the examiner stated, because "[a] trademark or trade name is used to identify a source of goods, and not the goods themselves." PTX-2E, at 478. The examiner explained that "[i]n the present case, the trademark/trade name is used to identify/describe acrylate/C10-30 alkyl acrylate cross-polymers, or high molecular weight co-polymers of acrylic

[43] The specification also states that the "emulsion stabilizing component advantageously is present in an amount effective to at least assist in stabilizing the cyclosporin component-containing emulsion," such as, "[f]or example, . . . in an amount in a range of about 0.01% by weight or less to about 1% by weight or more, preferably about 0.02% by weight to about 0.5% by weight, of the composition." E.g., '111 patent, col. 11, ll. 45-52.

acid and a long chain alkyl methacrylate cross-linked with allyl ethers of pentaerythritol." Id. at 479 (citing disclosure).

Following the examiner's rejection based on the use of the trade name Pemulen, the applicants amended the original claims to recite "acrylate/C10-30 alkyl acrylate cross-polymer" in place of "Pemulen." See PTX-2F, at 536-38 (claims 37, 44, 54, 60). The applicants advised the examiner that "no new matter has been added by this amendment." PTX-2F, at 541. The examiner found that substitution satisfactory, and all six patents subsequently issued using that term in place of the trade name "Pemulen."

In addressing the claim construction issue, the parties focus on expert testimony regarding how a person of skill in the art would understand the term "acrylate/C10-30 alkyl acrylate cross-polymer." Defendants' expert Dr. Hanes testified that a person of skill in the art would understand the cross-polymer term to have the meaning associated with "the conventional method of naming a polymer." Dkt. No. 472, Trial Tr. 62. As such, he testified, the term encompasses "a very large family of polymers"—"millions, if not many more" having "widely different properties." Id. at 63. The defendants contend that the patents fail to enable that broad class of compounds, as it would take considerable effort to determine which of those compounds would be suitable for use in an ophthalmic emulsion and which would not. On that ground, the defendants argue that all 13 of the asserted claims are invalid for lack of enablement.

Allergan responds that a skilled artisan in the field of ophthalmic formulations as of the September 2003 priority date for the Restasis patents would understand the term "acrylate/C10-30 alkyl acrylate cross-polymer" to refer to a small group of commercially available cross-polymers that are suitable for use in an ophthalmic emulsion. Those cross-polymers include several types of Pemulens, one of which is used in Restasis and in all of the defendants'

proposed generic products. In support of that construction, Allergan's expert Dr. Loftsson testified that to determine the meaning of the term "acrylate/C10-30 alkyl acrylate cross-polymer," a person of skill in the art of formulating ophthalmic emulsions would look to handbooks in the field of pharmaceutical formulations and related fields. One such handbook cited by Dr. Loftsson is E. Desmond Goddard & James V. Gruber, Principles of Polymer Science and Technology in Cosmetics and Personal Care (1999), PTX-1009. An appendix to that handbook, entitled "Encyclopedia of Polymers and Thickeners for Cosmetics," contains an entry for "Acrylate/C10-30 Alkyl Acrylate Crosspolymer," for which the handbook provides the trade names "Carbopol 1342, 1382 resins; Pemulen TR-1 TR-2 resins." Id. at 41. Asked why a person of skill in the art of pharmaceutical formulations would consult a handbook on polymers used in the cosmetics field, Dr. Loftsson explained that the process of formulating cosmetics "is very similar to formulation of pharmaceutical products. And pharmaceutical scientists frequently work in the cosmetic industry developing cosmetic product. . . . And it's quite normal to go into the cosmetic handbooks and look for ideas of new excipients that you could use." Dkt. No. 474, Trial Tr. 101. Based on the trade names used in the Encyclopedia of Polymers and Thickeners for Cosmetics, Dr. Loftsson testified that in the context of the Restasis patents a person of skill in the art would understand the term "acrylate/C10-30 alkyl acrylate cross-polymer" to mean "polymers like Carbopol, two types of Carbopol polymers, and then we have two types of Pemulen polymers." Dkt. No. 474, Trial Tr. 99.

In addition to Dr. Loftsson's testimony, Allergan elicited testimony from Dr. Olejnik as to the meaning of the cross-polymer limitation to a person of skill in the art. Dr. Olejnik noted that the Ding II patent referred to Pemulen as "a polymeric emulsifier having a CTFA [Cosmetics, Toiletries, and Fragrances Association] name of Acrylates/C10-30 Alkyl Acrylate

Cross-Polymer." Dkt. No. 469, Trial Tr. 167 (citing the Ding II patent, col. 5, ll. 32-35). He explained the reference to the CTFA by stating that Allergan researchers frequently looked to related art fields to discover appropriate excipients, and in particular that Allergan researchers used the CTFA databank as a source for excipients that could potentially be used in ophthalmic formulations. Dkt. No. 469, Trial Tr. 167-68.

Consistent with Dr. Olejnik's testimony, Allergan introduced another handbook relating to the use of polymers in emulsions, David B. Braun & Meyer R. Rosen, Rheology Modifiers Handbook (2000), PTX-1002. That handbook states that for personal care grades of cross-lined acrylic polymers, the Cosmetics, Toiletries, and Fragrances Association had assigned the name Carbomer to Carbopol and Acritamer products, and had assigned Pemulen products the name "Acrylates/C10-30 Alkyl Acrylate Cross-Polymer." Id. at 4-5.

Allergan introduced another dictionary of skin care and cosmetic ingredients, Natalia Michalun, Milady's Skin Care and Cosmetic Ingredients Dictionary (2d ed. 2001), PTX-1006. That dictionary defined the term "acrylate C10-30 alkyl crosspolymer" as "an emulsifier for oil-in-water emulsions with thickening and formula-stabilizing properties similar to a carbomer." Id. at 5. Thus, consistent with Dr. Olejnik's testimony, the three dictionaries and handbooks that Allergan introduced, which were specific to the related field of cosmetic formulations, used the term "acrylate/C10-30 alkyl acrylate cross-polymer" not as it would be used in the chemical arts, but much more narrowly, to refer to a specific set of commercially available polymers used as emulsifiers and emulsion stabilizers.

From the evidence before it, the Court finds that the cross-polymer limitation was not used in the Restasis patents to refer to all compounds that may be encompassed within the chemical structure described by the term. Understood simply as a chemical genus, the term

would include a wide variety of substances that may be toxic or otherwise unsuitable for ophthalmic use. See Dkt. No. 472, Tr. 124. To the contrary, the common specification suggests that such compounds were meant to be excluded from the scope of the patent:

> The presently useful compositions advantageously are ophthalmically acceptable. A composition, component or material is ophthalmically acceptable when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissues.

See, e.g., '111 patent, col. 4, ll. 19-24. Further evidence that the cross-polymer limitation in the Restasis patents was not intended to include any compound falling within the broad chemical class encompassed by the term "acrylate/C10-30 alkyl acrylate cross-polymer" is the statement in the common specification that "[u]seful emulsifier components may be selected from such components which are conventionally used and well known in the art." Id., col. 10, ll. 24-26.

Claims are construed as they would be understood by a person of skill in the art at the time of the invention. See Kopykake Enters. v. Lucks Co., 264 F.3d 1377, 1383 (Fed. Cir. 2001); Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1352-54 (Fed. Cir. 2000). Here, the person of skill is not a general chemist, but someone with experience in developing for designing formulations for ophthalmic treatments.

Based on the evidence presented at trial, the Court finds that a person of skill in the art would not understand the inventions claimed in the asserted Restasis patents to include all cross-polymers falling within the recited chemical structure, including those known to be toxic or otherwise unsuitable for use in an ophthalmic application. See Mitsubishi Chem. Corp. v. Barr Labs., Inc., 435 F. App'x 927, 935 (Fed. Cir. 2011) (rejecting a "claim construction that would allow a 'plainly toxic composition, such as a cleaning fluid or a pesticide,' to meet the limitations of [a] claim" covering a pharmaceutical composition). Rather, a person of skill would consider

the options to be quite limited, given the sensitivity of the eye and the need for administration to a human.

The evidence at trial showed that an ophthalmic formulator works within restrictive constraints and consults particular types of reference materials before proceeding. Dkt. No. 474, Trial Tr. 97 (Dr. Loftsson); see also Dkt. No. 469, Trial Tr. 166-68 (Dr. Olejnik). For that reason, the Court does not credit the testimony of the defendants' expert Dr. Hanes that a person of skill would understand the term to refer to the broad chemical genus.

The prosecution history supports a narrow construction of the cross-polymer term. The applicants drafted the cross-polymer term restrictively, limiting it to the term "Pemulen," by which the applicants clearly intended to refer to the small class of Pemulen polymers. It was only in response to the examiner's objection to the use of a trade name that the applicants substituted the formal name for the cross-polymer, as the examiner had suggested. There was no indication in the prosecution history that by amending the trade name "Pemulen" to the cross-polymer term, the applicants intended to effect a huge expansion of the scope of the claims to cover any cross-polymer falling within the chemical structure described by the term "acrylate/C10-30 alkyl acrylate cross-polymer." Instead, the Court finds that the applicants used that term as would persons skilled in the art of formulating emulsions for cosmetic or ophthalmic purposes, which would be limited to those cross-polymers known to be suitable for such uses, in particular, Pemulens.

The task of construing the cross-polymer limitation is rendered difficult by the circumstances in which that limitation made its way into the patents, and in particular the apparent haste on the part of the prosecutors of the applications to replace the term "Pemulen"

with another term acceptable to the examiner.[44] Notwithstanding the ambiguity introduced by the use of the chemical name for the class of cross-polymers, the Court is persuaded that the applicants intended merely to find a suitable substitute for the trade name Pemulen. The emulsion stabilizer was a tangential aspect of the invention, akin to the other claimed emulsifier, polysorbate 80, a specific compound identified in the claims by name. Based on the evidence that the term "acrylate/C10-30 alkyl acrylate cross-polymer" is used in the industry as the name for the group of Pemulen compounds, the Court concludes that the term should be read to have the same meaning as the trade name—Pemulen—that it replaced.

Allergan argues for a somewhat broader claim construction that would include both carbomers and Pemulen materials that existed as of the September 2003 priority date for the Restasis patents. Allergan's Post-Trial Findings of Fact and Conclusions of Law, Dkt. No. 494, ¶¶ 264, 269. While that construction would be consistent with Dr. Loftsson's testimony, it would be inconsistent with the Rheology Modifiers Handbook, which indicates that the CTFA had assigned the name "acrylates/C10-30 alkyl acrylate cross-polymer" to Pemulen products and the name Carbomer to other products. PTX-1002, at 4; see also Ding II patent, col. 5, ll. 32-33 ("Pemulen® is a polymeric emulsifier having a CTFA name of Acrylates/C10-30 Alkyl Acrylate Cross-Polymer.").

The issue of whether carbomers are included within the scope of the cross-polymer limitation is further complicated by the change in nomenclature made by the USP-NF in 2002, which is discussed in more detail in the next section. In brief, prior to 2002, Pemulen was the

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[44] The response to the October 17, 2013, office action, which included the amendments to the claims and a lengthy response to the examiner's other grounds of rejection, was filed less than a week after the office action, presumably because Allergan was eager to have the Restasis patents issue before the Ding I patent expired in May 2014.

trade name for a small group of compounds assigned the name Carbomer 1342 by the United States Pharmacopeia—National Formulary ("USP-NF"), which is published by the principal standard-setting organization in the pharmaceutical field. See PTX-493, PTX-494. That is how Pemulen was described both in the Ding II patent, col. 5, ll. 32-35, and in Allergan's Original NDA Filing submitted to the FDA, PTX-16L, at AGN_RES0007971-72. In April 2002, the USP-NF revised the nomenclature so that the product that carried the trade name Pemulen TR-2 became known as Carbomer Copolymer Type A. PTX-500, at 2; DTX-1517, at 4. That is the way Pemulen has been described since that time. See PTX-495; PTX-496; DTX-1523. Carbomer 1342 is now the USP-NF designation for the compound known as Carbopol 1342 NF Polymer. DTX-1522. Thus, references to "carbomer" prior to 2002 would include Pemulen, while references to "carbomer" after 2002 would not, at least according to the USP-NF's nomenclature for that group of polymers.

While there is room for debate as to whether the term "acrylate/C10-30 alkyl acrylate cross-polymer" in the Restasis patents covers certain specific emulsifiers other than Pemulen products (in particular, other carbomers that were known in 2003, as testified by Dr. Loftsson), it is clear to the Court that the cross-polymer limitation was not intended to encompass the entire class of all cross-polymers that would answer to the structure of cross-polymers described by the term "acrylate/C10/30 alkyl acrylate cross-polymer."

The defendants' enablement argument is predicated entirely on their claim construction argument. Because the Court has rejected the defendants' argument that the cross-polymer claim term must be construed to encompass any compound, made or imagined, that answers to the chemical structure described in the claims, the Court rejects the defendants' argument that the asserted claims of the Restasis patents are invalid for lack of enablement.

V. Noninfringement Based on the Cross-Polymer Limitation

Pivoting from their enablement argument, which is based on assigning the cross-polymer limitation the broadest possible construction, the defendants argue that if the cross-polymer limitation is not construed so broadly as to render the asserted claims invalid, it must be construed so narrowly that the defendants' products do not infringe. In making this argument, the defendants contend that the evidence shows that in 2005 Allergan changed the cross-polymer used in Restasis from one type of cross-polymer to another. For that reason, they contend, the cross-polymer used in Restasis at the time it was approved is a different product from the cross-polymer that is currently used in Restasis and that is designated for use in the defendants' ANDA products. The defendants contend that if the cross-polymer term is construed narrowly, i.e., to apply only to the particular cross-polymer that was used in the approved version of Restasis, then the defendants do not infringe.

The first problem with the defendants' argument is that the defendants did not raise this non-infringement argument at any point before Dr. Noecker's cross-examination at trial. See Dkt. No. 471, Trial Tr. 131-43. Under Rule 8-3(d) of the Patent Rules of the Eastern District of Texas, the defendants were required, within 14 days of the Initial Case Management Conference, to "provide to Plaintiff(s) the written basis for any defense of non-infringement for any patent referred to in Defendant(s) Paragraph IV Certification." That production was required to identify for each claim "those claim limitation(s) that are literally absent from the Defendant(s) allegedly infringing abbreviated New Drug Application." The defendants failed to inform Allergan of their non-infringement theory based on the purported change in the type of cross-polymer used in Restasis. For that reason, the Court holds that the defendants have waived their non-infringement claim based on the alleged change in the cross-polymer used in Restasis.

In any event, the evidence at trial shows that the actual cross-polymer used in Restasis did not change in 2005, and that the cross-polymer used in the tested version of Restasis is the same as the cross-polymer used in the current version of Restasis (and the same as the cross-polymer used in the defendants' proposed ANDA products). Only the name of the cross-polymer has changed; the actual compound used in the Restasis formulation, both at the time of the Phase 3 clinical trials and at the time of marketing, has remained the same.

The defendants point to testimony on cross-examination from Dr. Noecker, who acknowledged that in his report he stated, "I understand . . . that Allergan changed the co-polymer used in Restasis from carbomer 1342 to carbomer co-polymer type A." Dkt. No. 471, Trial Tr. 131-32. As the basis for that statement, Dr. Noecker relied on a report by Dr. Cory J. Berkland, an Allergan expert who did not testify at trial. The defendants argue that Carbomer 1342 is polymerized in benzene (a toxic substance), while Carbomer Co-polymer Type A, which carries the trade name Pemulen, is polymerized in ethyl acetate and cyclohexane (nontoxic substances), and thus the two cross-polymers are different. Dkt. No. 477, Trial Tr. 20.

The evidence, however, indicates that the change Allergan made regarding the cross-polymer used in Restasis was a change in name only; the cross-polymer material, including the solvents, remained the same. On redirect examination, Dr. Noecker testified that he had relied on Dr. Berkland's report for the proposition that "carbomer co-polymer type A is also an acrylate/C10-30 alkyl acrylate cross-polymer like carbopol 1342 and Pemulen TR2 because it is simply another name for Pemulen TR2." Dkt. No. 471, Trial Tr. 153. Based on Dr. Berkland's report, Dr. Noecker testified that "the change from carbomer 1342 to carbomer co-polymer type A" appeared to be "just a name change," and that to his knowledge the formulation of Restasis has never changed. Id.

Because the issue of the "two forms of Restasis" arose for the first time in this case during the cross-examination of Dr. Noecker, Allergan moved at the end of the trial to reopen the record to admit additional evidence on that issue. The Court granted Allergan's motion to the limited extent of permitting Allergan and the defendants to offer documentary material that had already been ruled admissible but had not yet formally been admitted into evidence. Dkt. No. 488.

The documentary evidence admitted following Allergan's motion to reopen the record confirms Dr. Noecker's testimony on redirect examination that the change in the cross-polymer used in Restasis was a change in name only. One of the exhibits, PTX-500, explains why. The exhibit, a publication by the Lubrizol Corporation, a manufacturer of cross-polymers, explains that the "traditional" cross-polymers were all polymerized using benzene as a solvent. The company later offered products polymerized in "more toxicologically preferred solvents" such as "ethyl acetate or a cosolvent mixture of ethylacetate and cyclohexane." PTX-500, at 1. As briefly discussed above, the USP-NF initially used the same generic name—Carbomer 1342—for certain cross-polymers whether they were polymerized in toxicologically preferred solvents or were polymerized in benzene. In 2002, the USP-NF assigned a different name to those polymers that were manufactured without the use of benzene. Thus, the polymers that were manufactured with the use of benzene retained the name "Carbomer 1342," while the polymers that were manufactured without benzene were, in 2002, assigned the name "Carbomer Co-polymer." DTX-1517, at 4. The USP-NF identified three types of Carbomer Co-polymers, Types A, B, and C, depending on their viscosity. The Carbomer Co-polymer with a 1% viscosity specification of 4500-13,500 was designated as Carbomer Co-polymer Type A. Id.

Allergan has pointed to evidence from B.F. Goodrich's product specifications for its Pemulen product, which supports Allergan's explanation of the differing names for the cross-polymer used in Restasis. The Goodrich product specification for the year 1994 refers to Pemulen TR-2 NF as meeting the USP-NF specifications for Carbomer 1342, even though Pemulen was manufactured in ethyl acetate and cyclohexane, not benzene. See PTX-493. The same was true of the Goodrich specification for Pemulen in the year 1998. See PTX-494. By 2002, although Pemulen continued to be manufactured in ethyl acetate and cyclohexane, the Goodrich specification for Pemulen provided that it met the USP-NF specifications for Carbomer Co-polymer Type A. See PTX-495; see also PTX-496 (Lubrizol's 2009 specification for Pemulen TR-2, stating that it met the USP-NF specifications for Carbomer Co-polymer Type A, that it was manufactured in ethyl acetate and cyclohexane, and that it contained only a trace amount of benzene).

The defendants' exhibits (DTX-1522 and DTX-1523) support Allergan's argument. They consist of Lubrizol's 2010 specifications for Pemulen TR-2 NF Polymer and Carbopol 1342 NF Polymer. The Pemulen polymer is stated to satisfy the USP-NF specifications for Carbomer Co-polymer Type A and is said to be manufactured with ethyl acetate and cyclohexane as solvents, while the Carbopol 1342 polymer is stated to satisfy the USP-NF specifications for Carbomer 1342 and is said to be manufactured with benzene as a solvent. Those documents thus show that Pemulen and Carbomer Co-polymer Type A are the same compound and are both manufactured with the same (non-benzene) solvents.

Finally, Allergan's NDA filing in February 1999 confirms what the B.F. Goodrich and Lubrizol specifications indicate. The NDA filing states that "Carbomer 1342, supplied from BF Goodrich Specialty Chemicals under the trade name Pemulen® TR-2, is polymerized in an ethyl

acetate/cyclohexane mixture without using benzene." PTX-16L, at AGN_RES0007971-72. The evidence thus shows that Restasis has been made with the same cross-polymer since its approval, whether under the name "Pemulen" or "Carbomer Co-polymer Type A."

The defendants next argue that there is a difference in viscosity between the product used in the tested version of Restasis and in the current version of Restasis (which uses the same cross-polymer as is specified for use in the defendants' proposed products). The evidence, however, indicates that is not so. In the B.F. Goodrich specification sheets for 1998, the viscosity for the Pemulen TR-2 NF was stated to be between 9,500 and 26,500 at 1% under test procedure 430. PTX-494. However, in the 2002 specification sheet from Noveon, Inc., the viscosity shown for Carbomer Co-polymer Type A, was stated to be between 4,500 and 13,500. PTX-495. That same viscosity was shown in the Official USP-NF Monograph of 2005 for Carbomer Co-polymer manufactured without the use of benzene. In particular, that monograph lists the viscosity for Carbomer Co-polymer Type A as 4,500 to 13,500. DTX-1517; see Dkt. No. 471, Trial Tr. 136-37. Likewise, in the specification sheets from Lubrizol in 2009 and 2010, the viscosity for Carbomer Co-polymer Type A is given as 4,500 to 13,500. PTX-496; DTX-1523. Thus, by the time Restasis was approved by the FDA, the viscosity range for Carbomer Co-polymer Type A (or Pemulen TR-2 NF) was the same (4,500 to 13,500) as it was in 2010. The evidence therefore does not support the defendants' contention that the viscosity of the cross-polymer component of Restasis changed in 2005 or at any other relevant time following its approval by the FDA.[45]

[45] In any event, the viscosity ranges for Pemulen TR-2 NF in 1998 and Carbomer Co-polymer Type A in 2002 overlap, and there was no evidence at trial that those differences in the permissible ranges of viscosity made a material difference in the cross-polymers. The only

Based on all the evidence before it, the Court finds that the cross-polymer used in Restasis has not been changed in a way that undermines Allergan's infringement case. The cross-polymer used in Restasis has been manufactured in ethyl acetate and cyclohexane from the outset, and the viscosity has not varied. Only the name of the cross-polymer has been changed. The defendants' non-infringement argument, based on the claim that a different cross-polymer has been used in Restasis since 2005, is therefore rejected.

In any event, the issue of infringement turns on the question whether the defendants' ANDA products are bioequivalent to the version of Restasis that was approved by the FDA. The evidence at trial shows that each of the defendants has represented to the FDA that their ANDA products are bioequivalent (and essentially identical in composition) to the tested version of Restasis. See Dkt. No. 471, Trial Tr. 22-37, 42-45, 47-51, 68-77; PTX-506; PTX-507; PTX-510; PTX-512; PTX-516; PTX-794; PTX-796; PTX-800; PTX-801; PTX-818; PTX-831; PTX-863; PTX-865; PTX-867; PTX-876; PTX-892; see also Dkt. No. 471, Trial Tr. 78-80. The Court finds that the evidence is sufficient to prove that the defendants' ANDA filings infringed the Restasis patents. Therefore, even if it were the case that the cross-polymer component of

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evidence that the defendants introduced regarding the viscosity issue was Allergan's citizen petition to the FDA, which included a passage noting that Restasis contains Carbomer Co-polymer Type A, which is a shear-thinning polymer whose viscosity decreases with increasing rates of shear. DTX-1355. The citizen petition objected to the FDA's failure to specify any method for measuring viscosity and its failure to prohibit a single-point viscosity measurement. To measure bioequivalence, according to the citizen petition, it would be necessary to test generic emulsions "at different rates of shear to ensure that their viscosity profiles match Restasis's viscosity throughout a range of shear rates." Id. That is a different matter from the question whether the different but overlapping viscosity ranges for Pemulen TR-2 NF in 1998 and Carbomer Co-polymer Type A as of 2002 rendered those products materially different for purposes of the Restasis formulation. Because there is no evidentiary basis from which to conclude that the two cross-polymer products were materially different, Allergan's evidence that the two products were the same, Dkt. No. 471, Trial Tr. 152-53, stands unrebutted.

Restasis had changed over time (other than simply as a matter of nomenclature), the Court would find that the defendants have satisfied all the requirements for infringement of the asserted Restasis patents under section 271(e)(2).[46]

CONCLUSION

Viewed from a broader perspective, the Court draws the following conclusions from the evidence in this case: There is no doubt that Allergan has invented a useful and successful pharmaceutical product. It has been richly rewarded for that invention in large measure because it was able to get patent protection for the invention in 1995 when the Ding I patent issued. Allergan had 20 years of patent protection for its invention and ultimately for Restasis, the commercial embodiment of that invention, which was clearly covered by Ding I.

Although Allergan kept continuation applications alive for some years after Restasis was approved by the FDA, it ultimately conceded to the PTO in 2009 that the claims of the

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[46] Aside from their argument as to the cross-polymer limitation, the defendants do not raise any challenge to Allergan's infringement allegations as to any of the asserted claims. Based on the evidence of the defendants' representations to the FDA regarding their ANDA products, the Court finds that Allergan has proved infringement of all the other limitations of the asserted claims, including the limitations as to therapeutic efficacy (claims 26 and 27 of the '111 patent; claims 13 and 14 of the '048 patent; claim 35 of the '930 patent; and all the asserted claims of the '191 patent), increasing and restoring tear production (all the asserted claims of the '048 patent; claim 35 of the '930 patent; and all the asserted claims of the '191 patent), the pH of the emulsion (claim 23 of the '048 patent and claim 25 of the '191 patent), the absence of a detectable concentration of cyclosporin in the blood (claim 11 of the '048 patent; claim 35 of the '930 patent; and claim 22 of the '191 patent), the reduction in adverse events (claims 21, 22, 23, 26, and 27 of the '191 patent), cyclosporin being the only peptide in the emulsion (all the asserted claims of the '111 patent), and the frequency of treatment (all the asserted claims of the '048 patent and all the asserted claims of the '191 patent). The Court's findings apply not only to Allergan's allegations of "artificial" infringement under section 271(e)(2), but also to direct infringement under section 271(a), induced infringement under section 271(b), and contributory infringement under section 271(c). Thus, the defendants' submission of their ANDAs has resulted in infringement of each of the asserted claims of the Restasis patents under section 271(e), and if the defendants sell their ANDA products, those products will infringe each of the asserted claims of the Restasis patents under sections 271(a), (b), or (c).

continuation applications that were directed to the Restasis formulation would have been obvious in light of the Ding I patent. However, in 2013, a few months before the expiration date of the Ding I patent, Allergan returned to the PTO, withdrew its concession of obviousness, and renewed its effort to obtain further patent protection for Restasis.

Allergan's theory in prosecuting the new applications was that the Restasis formulation, although falling within the scope of the Ding I patent, surprisingly produced exceptionally good results, so much so that the particular formulation for Restasis was entitled to patent protection even though that formulation fell within the scope of the ranges of values disclosed and claimed in Ding I. Allergan persuaded the examiner to issue the patent by way of a presentation that was more advocacy than science. The presentation suggested that the Restasis formulation resulted in efficacy levels up to eight times as great as would be expected based on studies of the formulations disclosed in the Ding I patent. In fact, a closer examination of the results of the clinical studies on which Allergan relied makes it clear that the presentation to the PTO substantially overstated the difference between the clinical results obtained with the Ding formulations and the clinical results obtained with the Restasis formulation. The actual clinical results, interpreted properly, show no significant difference in efficacy between the Restasis formulation and the 0.1% formulation that was Example 1D of the Ding I patent.

At trial, Allergan presented essentially the same theory—that the Restasis formulation produced results that were unexpected in light of the prior art—albeit without urging upon the Court the evidence that Allergan had presented to the PTO. In so doing, Allergan has had to deal with the problem that a considerable amount of highly pertinent prior art had accumulated by the 2003 priority date of the Restasis patents. Not only does the Ding I patent pose a problem for

Allergan, but the papers by Sall and Stevenson revealed a great deal of information about the studies on which Allergan relies to make its "unexpected results" case.

To the extent that Allergan's argument turns on the putative difference between the results obtained in the Phase 2 and Phase 3 studies, the argument is based on a shaky foundation: the contention that the small Phase 2 study demonstrated clearly superior performance by the 0.1% cyclosporin/1.25% castor oil formulation as compared to the 0.05% cyclosporin/0.625% castor oil formulation. To the extent that Allergan's argument is based on the contention that the 0.05% cyclosporin/1.25% castor oil formulation would not have been expected to be effective after the percentage of castor oil in the formulation was doubled from the percentage used in the 0.05% cyclosporin formulation in the Ding I patent (and in the Phase 2 study), the argument ignores the evidence in the prior art that castor oil has beneficial effects in treating dry eye, which it would be reasonable to expect could offset any effects of the decrease in the ratio of cyclosporin to castor oil. Allergan's reliance on the pharmacokinetic evidence that the thermodynamic activity of cyclosporin is reduced in the presence of greater amounts of castor oil ignores the dose-response evidence in the prior art indicating that, even if the amount of cyclosporin available to the ocular tissue was reduced in the 0.05% cyclosporin/1.25% castor oil formulation, the clinical efficacy of the drug was the same.

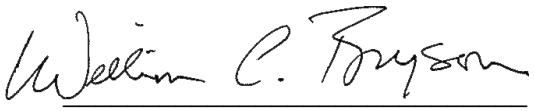
While Allergan has pointed to evidence of objective considerations such as commercial success and long-felt unmet need, the force of that evidence is considerably blunted by the fact that, based on protection from a succession of patents, Allergan was able to foreclose competition in cyclosporin/glyceride emulsion formulations from the early 1990s until 2014. And the issuance of the Restasis patents has barred any direct competition for Restasis since

then. The evidentiary value of the objective consideration evidence has thus been considerably weakened by the existence of blocking patents during the critical period.

In this setting, based on the extensive amount of pertinent prior art and the Court's factual assessment of Allergan's showing of unexpected results, the Court has concluded that Allergan is not entitled to renewed patent rights for Restasis in the form of a second wave of patent protection. The Court therefore holds that while Allergan has proved by a preponderance of the evidence that the defendants have infringed the asserted claims of the Restasis patents, the defendants have proved by clear and convincing evidence that the asserted claims of the Restasis patents are invalid for obviousness.

IT IS SO ORDERED.

SIGNED this 16th day of October, 2017.



WILLIAM C. BRYSON
UNITED STATES CIRCUIT JUDGE