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Topical Cyclosporine 0.05% for the Prevention of Dry Eye Disease Progression

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Abstract

Purpose: To assess the prognosis of dry eye in patients treated with cyclosporine 0.05% or artificial tears by using the International Task Force (ITF) guidelines.
Methods: This was a single-center, investigator-masked, prospective, randomized, longitudinal trial. Dry eye patients received twice-daily treatment with either cyclosporine 0.05% (Restasis®; Allergan, Inc., Irvine, CA; $n = 36$) or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA; $n = 22$) for 12 months. Disease severity was determined at baseline and month 12 according to the consensus guidelines developed by the ITF. Dry eye signs and symptoms were evaluated at baseline and months 4, 8, and 12.
Results: Baseline sign and symptom scores and the proportion of patients with the disease severity level 2 or 3 were comparable in both groups ($P > 0.05$). At month 12, 34 of 36 cyclosporine patients (94%) and 15 of 22 artificial tear patients (68%) experienced improvements or no change in their disease severity ($P = 0.007$) while 2 of 36 cyclosporine patients (6%) and 7 of 22 artificial tears patients (32%) had disease progression ($P < 0.01$). Cyclosporine 0.05% improved Schirmer test scores, tear breakup time, and Ocular Surface Disease Index scores throughout the study, with significant ($P < 0.01$) differences compared with artificial tears being observed at months 8 and 12.
Conclusions: Treatment with cyclosporine 0.05% may slow or prevent disease progression in patients with dry eye at severity levels 2 or 3.

Introduction

Patients with dry eye disease suffer from ocular irritation often accompanied by vision impairment, which limits important daily activities and negatively impacts quality of life (QoL).[1–3] The prevalence of dry eye disease is estimated to be from 5% to >30%.[4,5] The largest US cross-sectional survey studies, the Women's Health Study (WHS) and the Physician Health Study (PHS), indicated that the prevalence of dry eye disease among women and men aged over 50 years is 7.8% and 4.3%, respectively. Using this prevalence data, ~4.9 million Americans aged over 50 years are estimated to be affected by dry eye disease.[6,7]

The diagnosis and treatment of dry eye is challenging.[8] The Wilmer Eye Institute at Johns Hopkins University recently invited the International Task Force (ITF) of 17 dry eye experts to create guidelines for the diagnosis and treatment of dry eye disease by using a Delphi consensus technique.[9] The ITF panel categorized dry eye disease severity into 4 levels (Table 1), with increasing severity from 1 to 4, and developed consensus treatment guidelines. The level of disease severity was considered the most important factor in determining the appropriate range of therapeutic options.[9] While counseling, education, and preserved artificial tears were recommended for the management of patients diagnosed at severity level 1, unpreserved artificial tears, topical cyclosporine, and/or corticosteroids were recommended for patients at severity level 2. Punctal plugs, oral tetracyclines, systemic immunomodulators, and surgery were reserved for the management of dry eye patients diagnosed at severity levels 3 and 4.[9]

A key recommendation of the ITF panel was the use of topical anti-inflammatory therapy in patients with clinically apparent ocular surface inflammation.[9] This recommendation stemmed from the recent evidence indicating that inflammation plays a major role in the disease etiology and may be a unifying mechanism that underlies dry eye

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TABLE 1. CRITERIA USED TO DETERMINE THE LEVELS OF DRY EYE SEVERITY ACCORDING TO ITF GUIDELINES[8]

	Symptoms	*Signs*	*Staining*
Level 1	Mild to moderate	Mild/moderate conjunctival signs	None
Level 2	Moderate to severe	Tear film signs, visual signs	Mild punctate corneal and conjunctival staining
Level 3	Severe	Corneal filamentary keratitis	Central corneal staining
Level 4	Severe	Corneal erosions, conjunctival scarring	Severe corneal staining

Disease severity is categorized into 4 levels based on the severity of symptoms and signs. At least one sign and one symptom of each category should be present to qualify for the corresponding level assignment.

disease.[10–12] Therefore, it was suggested that the chronic use of safe anti-inflammatory therapies that normalize tear film composition early in the disease process may have the potential to slow, prevent, or reverse dry eye progression.[13]

Ophthalmic cyclosporine 0.05% emulsion (Restasis®; Allergan, Inc., Irvine, CA) is the only anti-inflammatory medication approved by the Food and Drug Administration to increase tear production in dry eye patients.[14] In T lymphocytes, cyclosporine binds to cyclophilin A and inhibits calcineurin-catalyzed dephosphorylation of the nuclear factor for T-cell activation.[15,16] Cyclosporine thereby inhibits IL-2 transcription, which upon secretion stimulates T-cell division by a self-propagating autocrine and paracrine loop.[16] In humans, topical administration of cyclosporine 0.05% has been shown to decrease the number of activated T cells and expression of inflammatory markers in the conjunctiva of dry eye patients.[17,18] These findings suggest that topical cyclosporine 0.05% targets the underlying inflammatory processes in dry eye disease. Therefore, chronic treatment with cyclosporine 0.05% may offer the potential to alter the course of dry eye disease.

Wilson and Stulting recently evaluated the clinical applicability of the ITF guidelines.[13] Physicians participating in that study successfully implemented the ITF guidelines for diagnosis and treatment of dry eye patients.[13] Using the ITF guidelines, this study was designed to assess the prognosis of dry eye disease in patients treated with cyclosporine 0.05% or artificial tears.

Methods

Study design

This was a single-center, investigator-masked, randomized, prospective, longitudinal clinical trial. The study was approved by the Western institutional review board in Olympia, WA, and was registered with ClinicalTrials.gov (identifier # NCT00567983). Inclusion criteria were of age 18 years or older, diagnosis of dry eye without lid margin disease or altered tear distribution and clearance, and a disease severity of level 2 or 3 as defined by the ITF guidelines (Table 1).[9] Primary exclusion criteria were prior use of topical cyclosporine 0.05% within the last year, topical or systemic use of anti-inflammatory or anti-allergy medications, active ocular infection or inflammatory disease, or uncontrolled systemic disease that can exacerbate dry eye disease. Patients who wore contact lenses were also excluded from the study. All participating patients signed a written consent form before initiation of the study-specific procedures.

Patients were randomly assigned in a 3:2 ratio to twice-daily treatment with either cyclosporine 0.05% or artificial tears (Refresh Endura®; Allergan, Inc., Irvine, CA) in both eyes for 12 months. The randomization ratio was an empirical estimation due to lack of adequate epidemiological information to conduct power calculations prior to initiating the study. Randomization was performed by a statistical program and was overseen by the research coordinator. Patients were enrolled in the study and initiated therapy after screening and randomization on the same day at the baseline visit (month 0). All patients were allowed to utilize rescue artificial tears as needed if discomfort was experienced. The primary objective of this study was to assess the potential of topical cyclosporine 0.05% therapy to halt or slow disease progression relative to control at month 12 based on the ITF severity categorization (Table 1). The secondary outcome variables were the changes in dry eye signs and symptoms. The study was conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Disease severity and dry eye signs and symptoms

Disease severity was assessed according to the ITF consensus guidelines at baseline and month 12 (Table 1).[9] Patients were evaluated for signs and symptoms of dry eye by Schirmer test with anesthesia, tear breakup time (TBUT), ocular surface staining, and Ocular Surface Disease Index (OSDI) at baseline (month 0) and after receiving the study treatments at months 4, 8, and 12. In each study visit, TBUT was evaluated first, followed by ocular surface staining and Schirmer test, respectively. The TBUT was measured using fluorescein dye. Ocular surface damage was assessed by the Oxford method using sodium fluorescein to stain the cornea and lissamine green to stain the nasal and temporal bulbar conjunctiva.[19] The scoring scale for ocular staining was 0 to 5 in cornea, 0 to 5 in temporal conjunctiva, and 0 to 5 in nasal conjunctiva, with 0 representing no staining and 5 representing severe staining. These individual scores were then summed for the total Oxford score, which ranged from 0 to 15. The change from baseline was calculated by subtracting the baseline score from the months 4, 8, and 12 scores. The symptoms of ocular irritation and their impact on visual functioning was assessed by OSDI, a validated 12-item questionnaire, on a scale of 0 to 100 with 0 representing asymptomatic and 100 representing severe debilitating dry eye disease.[20]

Goblet cell density

The density of goblet cells in bulbar conjunctiva was evaluated at baseline and month 12. Impression cytology was performed in both eyes after evaluation of TBUT, ocular staining, and Schirmer test. Goblet cells were collected on cellulose acetate filters (HAWP 304 FO; Millipore Corp., Billerica, MA). The filters were fixated in glacial acetic acid, formaldehyde, and 70% ethanol and subsequently stained with a modified periodic acid–Schiff Papanicolaou stain. Goblet cells were counted in 5 (400 × 400 mm) representative microscopic fields on each filter.[21]

Statistical analyses

Patients who completed 12 months of treatment were included in the analyses. The results were presented as mean ± SD. Intergroup comparisons of categorical variables were performed using the chi-square or Fisher's exact test. Continuous variables were analyzed using nonparametric tests (Mann–Whitney tests for between-group comparisons and Wilcoxon signed rank tests for within-group comparisons). A P value < 0.05 was considered a statistically significant difference. Statview software (SAS Institute, Cary, NC) was used for all analyses.

Results

Patient disposition and disease characteristics

Of 74 patients enrolled between February 2006 and January 2007, 58 patients completed the 12-month study and were included in the analyses (Table 2). Forty-one patients were female and 17 patients were male. The distribution of patients with disease severity of level 2 or 3 was similar in both treatment groups at baseline. Approximately two-thirds of dry eye patients in both groups were diagnosed at severity level 2, while one-third of patients was diagnosed at severity level 3 (Table 2). There were no significant between-group differences in the mean age ($P = 0.667$) or distribution of gender ($P = 0.800$).

Sixteen patients discontinued the study. The number of discontinuations was significantly higher among patients treated with artificial tears compared with those treated with cyclosporine 0.05% (11 vs. 5; $P = 0.028$; Table 2). Of 11 discontinuations in the artificial tear group, 9 patients discontinued the study because of discomfort upon instillation, and 2 patients were lost to follow-up or moved. Seven of these patients had a disease severity of level 2, and 4 patients had a disease severity of level 3. Of the 5 discontinuations in the cyclosporine group, 2 patients discontinued the study because of discomfort upon instillation while 3 were lost to follow-up or moved. Three of these patients had a disease severity of level 2, and 2 patients had a disease severity of level 3.

Disease severity

At month 12, significantly more patients treated with artificial tears had more severe signs and symptoms of disease than did those treated with cyclosporine 0.05% and, therefore, were categorized as progressing to a higher disease severity level (7 of 22 [32%] patients vs. 2 of 36 [6%], respectively; $P < 0.007$; Fig. 1). In contrast, a greater percentage of patients treated with cyclosporine 0.05% had less severe signs and symptoms of disease and were categorized as improving to a lower disease severity level (14 of 36 [39%] patients vs. 4 of 22 [18%] patients, respectively). This difference, however, was not statistically significant ($P = 0.098$). When combined with those who did not have a change in the disease severity levels at month 12, significantly more patients treated with cyclosporine 0.05% had either improvements or no change in disease severity than did those treated with artificial tears (34 of 36 [94%] patients vs. 15 of 22 [68%] patients, respectively; $P = 0.007$).

Schirmer test scores

The mean baseline Schirmer test score was 7.7 ± 0.6 mm in patients randomized to artificial tears and 7.9 ± 1.2 mm

TABLE 2. PATIENTS' DISPOSITION AND DISEASE CHARACTERISTICS

	Artificial Tear	*Cyclosporine 0.05%*
Patients (*n*)		
Enrolled in study	33	41
Discontinued study	11[a]	5[b]
Completed study	22	36
Mean age[c] ± SD, years	48.2 ± 6.3	47.5 ± 5.9[d]
Range	39–59	30–57
Gender[c], *n* (%)		
Female	16 (73)	25 (69)[e]
Dry eye severity at baseline,[c] *n* (%)		
Level 2	15 (68)	24 (67)
Level 3	7 (32)	12 (33)

[a]Nine patients discontinued the study because of discomfort upon instillation. Two patients were lost to follow-up or moved. $P = 0.028$ compared to patients who received cyclosporine 0.05%.

[b]Two patients discontinued the study because of discomfort upon instillation. Three patients were lost to follow-up or moved.

[c]For patients who completed 12-month study.

[d]$P = 0.667$ compared to the mean age of patients who received artificial tears.

[e]$P = 0.800$ compared to the artificial tear group.

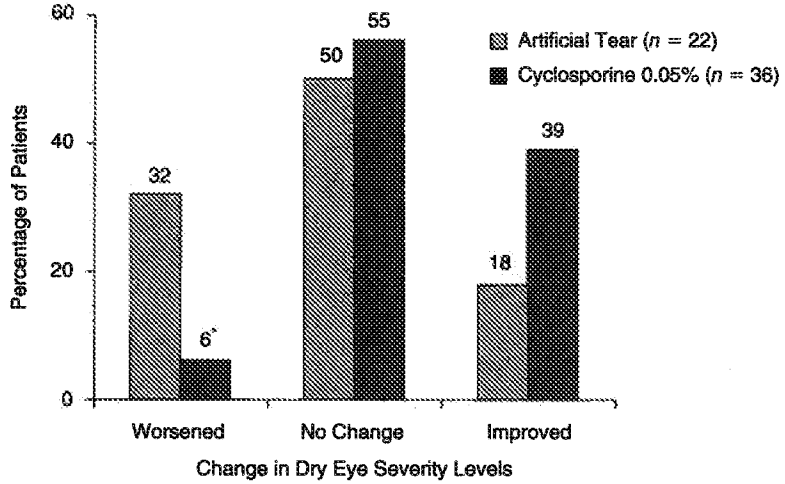

FIG. 1. Changes in dry eye severity at month 12 compared with baseline. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Disease severity was assessed according to the International Task Force (ITF) consensus guidelines at baseline and month 12. The changes in disease severity levels were categorized as worsened, no change, or improved when a patient had a, respectively, higher, same, or lower disease severity level at month 12 compared with baseline. *$P < 0.007$ compared with the treatment with artificial tears.

in patients randomized to cyclosporine 0.05% ($P = 0.625$). Patients treated with artificial tears did not have a significant change in their Schirmer test scores throughout the study, whereas those treated with cyclosporine 0.05% had increasingly higher mean Schirmer test scores at each follow-up visit. The mean Schirmer test scores of patients treated with cyclosporine 0.05% were significantly greater than those of patients treated with artificial tears at month 8 (9.1 ± 1.0 mm vs. 7.5 ± 1.1 mm; $P < 0.001$) and month 12 (9.8 ± 1.0 mm vs. 7.6 ± 1.1; $P < 0.001$; Fig. 2).

TBUT

The mean baseline TBUT was 5.0 ± 0.8 s in patients randomized to artificial tears and 4.9 ± 0.8 s in patients randomized to cyclosporine 0.05% ($P = 0.550$). The mean TBUT of patients treated with artificial tears slightly decreased throughout the study, whereas patients treated with cyclosporine 0.05% had increasingly longer mean TBUT at each follow-up visit (Fig. 3). The mean TBUT of patients treated with cyclosporine 0.05% was significantly longer than those of patients treated with artificial tears at months 8 (6.2 ± 1.4 s vs. 4.6 ± 0.6 s; $P = 0.001$) and 12 (6.5 ± 1.1 s vs. 4.6 ± 0.7 s; $P < 0.001$).

Ocular surface staining scores

At baseline, patients randomized to cyclosporine 0.05% or artificial tears had similar mean Oxford staining scores

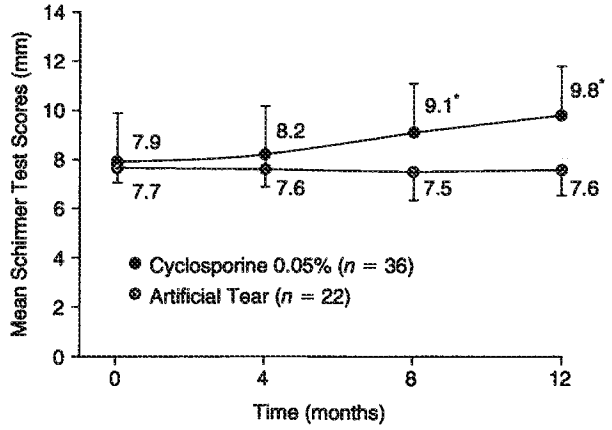

FIG. 2. Schirmer test scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Schirmer I test was performed with anesthesia at indicated study visits. *$P < 0.001$ compared with patients treated with artificial tears.

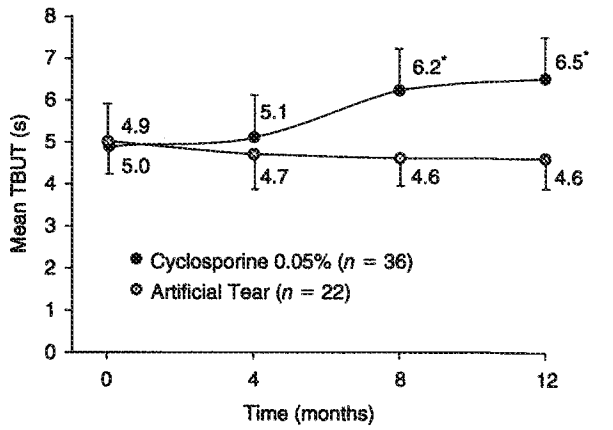

FIG. 3. TBUT. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Tear breakup time Tear breakup time (TBUT). was measured with fluorescein dye at indicated study visits. *$P \leq 0.001$ compared with patients treated with artificial tears.

TABLE 3. MEAN OCULAR SURFACE STAINING SCORES

	Artificial tear (n = 22)	*Cyclosporine 0.05% (n = 36)*	*P*
Baseline	7.86 ± 1.13 (NA)	8.44 ± 0.94 (NA)	0.056 (NA)
Month 4	7.73 ± 0.99 (–0.12 ± 0.64)	8.31 ± 0.95 (–0.13 ± 0.35)	0.036 (0.787)
Month 8	7.53 ± 1.01 (–0.25 ± 0.94)	7.78 ± 0.93 (–0.64 ± 0.63)	0.576 (0.087)
Month 12	7.54 ± 0.91 (–0.32 ± 0.94)	7.28 ± 1.28 (–1.19 ± 1.36)	0.223 (0.011)

Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Ocular surface damage was assessed at indicated times by the Oxford method. The mean changes from baseline and corresponding *P* values are indicated in brackets.[a] The change from baseline was calculated by subtracting the baseline score from the month 4, 8, or 12 scores.

NA = not applicable.

[a]The changes form baseline were paired comparisons. If a data point was missing, the baseline was also excluded from that calculation.

(8.4 ± 0.9 vs. 7.9 ± 1.1; $P = 0.056$; Table 3). At month 4, patients treated with cyclosporine 0.05% had significantly higher mean staining scores than those treated with artificial tears (8.3 ± 1.0 vs. 7.7 ± 1.0; $P < 0.036$). There was no between-group difference in ocular staining at months 8 and 12 (Table 3). Nonetheless, the mean improvement from baseline in the ocular staining scores of patients treated with cyclosporine 0.05% was significantly greater than of those treated with artificial tears at month 12 (1.2 ± 1.4 vs. 0.3 ± 0.9, respectively; $P = 0.011$; Table 3). These findings indicate that cyclosporine 0.05% improved ocular surface staining significantly more than did artificial tears at month 12 compared with baseline.

OSDI Scores

Patients randomized to artificial tears or cyclosporine 0.05% had similar OSDI scores at baseline (19.1 ± 1.9 and 18.9 ± 2.9, respectively; $P = 0.571$). The mean OSDI scores of patients treated with artificial tears remained unchanged throughout the study (Fig. 4). Patients treated with cyclosporine 0.05%, however, had increasingly lower OSDI scores at each study visit, with the scores at months 8 and 12 being significantly lower than those of patients treated with artificial tears (17.4 ± 3.4 vs. 19.6 ± 1.6 at month 8; $P = 0.011$ and 14.9 ± 4.2 vs. 19.7 ± 2.0 at month 12; $P < 0.001$).

Goblet cell density

At baseline, patients randomized to artificial tears or cyclosporine 0.05% had similar mean goblet cell density in bulbar conjunctiva (95.8 ± 12.5 cells and 93.6 ± 9.4 cells, respectively; $P = 0.446$; Fig. 5). By month 12, goblet cell density was significantly higher in patients treated with cyclosporine 0.05% than those treated with artificial tears (116.8 ± 14.8 cells vs. 92.7 ± 11.0 cells; $P < 0.001$).

Safety

No adverse events attributable to the study medications were reported other than discomfort upon instillation during the study.

Discussion

Dry eye is a multifactorial disorder of the tears and the ocular surface that results in tear film instability and symptoms of discomfort and visual disturbance.[22] Traditionally, treatment of dry eye has been palliative and largely based on over-the-counter artificial eyedrops and lubricating ointments.[23] The vast majority of patients seek new therapies after using several over-the-counter products over years.[23] However, it is not known if dry eye severity progresses through the course of disease during the years. Recently developed ITF guidelines provide a clinical standard for

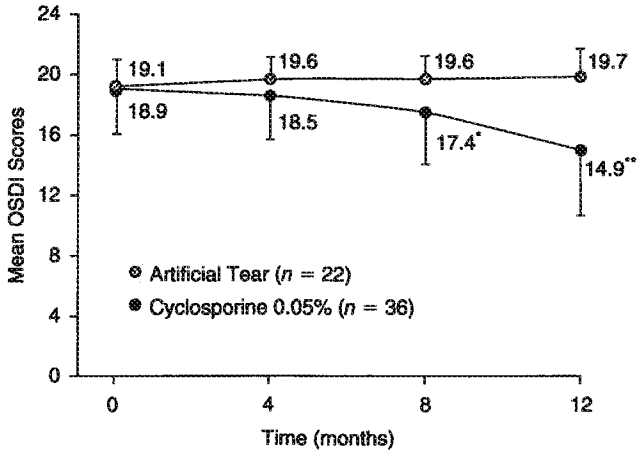

FIG. 4. Ocular Surface Disease Index (OSDI) scores. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Dry eye signs and symptoms were assessed by the self-reported OSDI questionnaire at indicated study visits. *$P < 0.011$ and **$P < 0.001$ compared with patients treated with artificial tears at months 8 and 12, respectively.

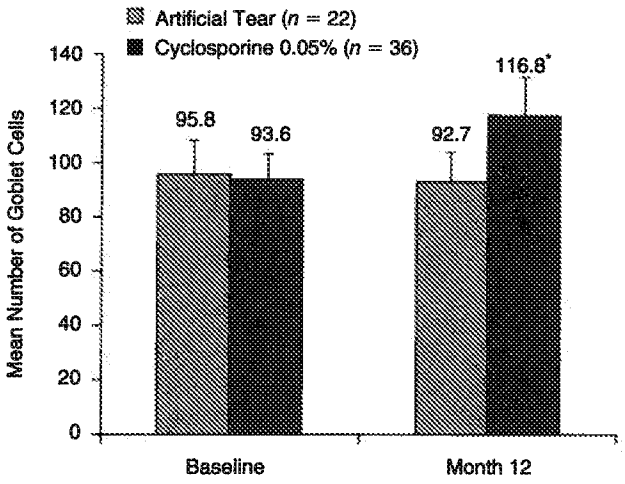

FIG. 5. Conjunctival goblet cell density at baseline and month 12. Patients were treated with cyclosporine 0.05% or artificial tears for 12 months. Conjunctival goblet cells were collected by impression cytology and counted following staining with modified periodic acid–Schiff Papanicolaou at baseline and month 12. *$P < 0.001$ compared with artificial tears at month 12.

categorization of dry eye patients based on the disease severity and thereby allow longitudinal studies to evaluate the progression of dry eye disease. This study not only sought to assess the progression of dry eye disease in patients treated with artificial tears, but also evaluated the impact of cyclosporine 0.05% therapy in modulating the course of dry eye disease.

Treatment of dry eye patients with cyclosporine 0.05% improved Schirmer test scores, TBUT, conjunctival goblet cell density, ocular surface staining scores, and OSDI scores throughout the study. Treatment with artificial tears was not effective in improving the signs and symptoms of dry eye disease. Similar to these findings, several other studies demonstrated that cyclosporine 0.05% significantly increased tear production, decreased the intensity of ocular staining, and decreased the severity of symptoms in patients with moderate to severe dry eye.[24,25] A recent prospective study indicated that cyclosporine 0.05% therapy significantly improved signs and symptoms in patients at all stages of dry eye disease: mild, moderate, and severe.[26] Other studies have shown that treatment with cyclosporine 0.05% also increased conjunctival goblet cell density in patients with dry eye disease.[21,27]

Physicians participating in a study to develop treatment regimens based on the ITF consensus guidelines for newly diagnosed dry eye patients chose to treat over 40% of patients at severity level 1 with the severity level 2 treatments (ie, unpreserved tears and topical cyclosporine 0.05%).[13] Hence, the use of ITF guidelines resulted in greater focus on treatment of the disease at early stages. This shift in the patterns of anti-inflammatory therapy use stems from the notion that early interruption of inflammatory cycles may be instrumental in preventing disease progression.[13] The impact of dry eye in limiting daily activities and causing discomfort is known to become clinically more significant as the disease progresses from mild to moderate in severity.[2]

In addition to alleviating dry eye signs and symptoms, topical cyclosporine 0.05% therapy appears to be capable of slowing the rate of disease progression. Reassessment of patients at the end of the study period (month 12) indicated that a greater number of cyclosporine patients compared with the artificial tear patients (94% vs. 68%) had improvements or no change in their disease severity status, and far fewer (6% vs. 32%) experienced disease progression. These findings suggest the progressive nature of dry eye disease and indicate that dry eye patients may benefit from cyclosporine 0.05% therapy by achieving disease stabilization or a slower rate of progression. A recent retrospective study provided evidence that cyclosporine 0.05% therapy may change the course of dry eye disease. In that study, 8 chronic dry eye patients diagnosed at severity level 2 or 3 were free of signs and symptoms of dry eye disease for a minimum of 1 year after completing a 6- to 72-month course of cyclosporine 0.05% therapy.[28]

In some patients, dry eye is a difficult-to-treat disease that requires long-term anti-inflammatory therapy. The safety profile of a topical anti-inflammatory agent and its suitability for long-term use is, therefore, a key factor in successful management of dry eye disease. Topical corticosteroids have been effective in alleviating the signs and symptoms of dry eye following short-term use (2–4 weeks).[29,30] Prolonged administration of topical corticosteroids is complicated by the associated adverse events including elevation of intraocular pressure, defects in visual acuity and fields of vision, cataract formation, and increased risk of ocular infections.[29,31] Topical cyclosporine 0.05%, however, appears to be safe for a long-term use. Several clinical studies demonstrated that cyclosporine 0.05% was well tolerated for up to 3 years with most adverse events being transient in nature and mild to moderate in severity.[24,25,32]

The present study had a number of limitations. The sample size was small, as this was a pilot study to assess the feasibility of the study design. It should also be noted that the differences between the treatment groups reported in this study can be applied only to the use of Refresh Endura® as the artificial tears. Other artificial tears may have variable efficacies in alleviating the signs and symptoms of dry eye.

Strategies to treat dry eye disease are evolving as our understanding of dry eye as a tear volume insufficiency condition is changing to a disease of abnormal tear film composition with proinflammatory characteristics.[10,33,34] The findings of the current study are the first evidence indicating that dry eye can be progressive in patients treated with artificial tears alone, whereas topical anti-inflammatory therapy with cyclosporine 0.05% may slow or prevent the disease progression in patients with dry eye at severity level 2 or 3. Large-scale, controlled studies are warranted to confirm these findings.

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EXHIBIT F

The Impact of Dry Eye Disease on Visual Performance While Driving

NATHALIE DESCHAMPS, XAVIER RICAUD, GHISLAINE RABUT, ANTOINE LABBÉ, CHRISTOPHE BAUDOUIN, AND ALEXANDRE DENOYER

• PURPOSE: **A specific simulator was used to assess the driving visual performance in patients with dry eye disease (DED) and to determine clinical predictors of visual impairments while driving.**

• DESIGN: **Prospective case-control study.**

• METHODS: **The study was conducted in the Center for Clinical Investigation of Quinze-Vingts National Ophthalmology Hospital, Paris, France. Twenty dry eye patients and 20 age- and sex-matched control subjects were included. Vision-related driving ability was assessed using a specific driving simulator displaying randomly located targets with a progressive increase in contrast to be identified. Other examinations included clinical examinations, serial measurements of corneal higher-order aberrations (HOAs), and vision-related quality-of-life questionnaire (Ocular Surface Disease Index [OSDI]). Data collected during driving test (ie, the number of targets seen, their position, and the response time) were compared between groups and analyzed according to clinical data, aberration dynamics, and quality-of-life index.**

• RESULTS: **The percentage of targets missed as well as average response time were significantly increased in DED patients as compared with controls ($P < .01$). More specifically, the visual function of DED patients was more impaired in specific situations, such as crossroad or roundabout approaches. In DED patients, the response time was found to positively correlate with the progression index for HOAs ($P < .01$) and with the OSDI "symptoms" subscale ($P < .05$).**

• CONCLUSIONS: **Degradation of ocular optical qualities related to DED is associated with visual impairments during driving. This study objectively has demonstrated the impact of tear film–related aberration changes on activities of daily living in DED. (Am J Ophthalmol 2013;156: 184–189. © 2013 by Elsevier Inc. All rights reserved.)**

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DRY EYE DISEASE (DED) IS RECOGNIZED AS a growing public health problem and one of the most frequent reasons for seeking eye care. The DED definition has evolved with recent epidemiologic studies as well as a better understanding of the pathophysiology of the disease. It is estimated to affect from 5% to over 30% of the population, depending on the diagnostic criteria.[1] This common health problem is likely to be overlooked because it tends not to be a common cause of visual morbidity as standardly measured. Nevertheless, there is increasing evidence that DED is a major cause of visual disturbance, which degrades the quality of everyday life and can impact health status.[2]

According to a recent overview arising from the 2007 International Dry Eye Workshop, DED causes damage to the ocular surface and symptoms of ocular discomfort associated with impaired visual quality.[3] Indeed, patients with DED often report vision-related difficulties in doing daily activities. In clinical practice, the main difficulty in managing DED stems from the variability of the symptoms, the lack of a single reliable diagnostic test, and weak correlations between clinical tests, optical and biological examinations, and patient-reported deterioration in quality of life.[4–6] The precorneal tear film plays an important role in ocular optical quality since it is the most anterior refractive surface of the eye.[7,8] In the majority of patients with DED, the visual acuity is still 20/20 as standardly measured, but instability of the tear film introduces wavefront higher-order aberration (HOA) changes that always contribute to a decrease in the quality of vision.[9,10] Our team recently demonstrated that a specific analysis of the time course of HOAs provides objective and quantitative data that are correlated with both clinical signs and patient-reported outcomes, raising the possibility of using this instrument as a new surrogate marker for the disease.[11]

Beyond conventional clinical examination and visual acuity measurement, a specific evaluation of the visual function in daily living tasks is now required to better define the impact of the disease on this population's health status but also to better assess eligibility or changes over time in clinical trials. Although DED patients commonly complain of difficulties in doing vision-related daily activities, as previously reported using quality-of-life questionnaires,[12] no study has been conducted to determine whether or not DED could be responsible for an objective decrease in visual performance while driving. The present study addresses the impact of DED on a crucial daily

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activity of modern living. A driving simulator dedicated to visual function evaluation was used in patients with DED and in age- and sex-matched healthy controls in order to better specify the relationship between driving difficulties, objective ocular signs and optical degradation, and patient-reported vision-related quality of life.

METHODS

• PATIENTS: The study was conducted in the Clinical Center for Investigation of Ocular Surface Pathology (Quinze-Vingts National Ophthalmology Hospital, National Institute for Health and Medical Research 503, Paris, France) in accordance with the Declaration of Helsinki, Scotland amendment, 2000. Previous approval was obtained from the National Ethical Research Committee (Comité de Protection des Personnes Ile de France V, agreement number 10793). All patients gave informed consent to participate in this clinical research study. Twenty white patients with DED and 20 white age- and sex-matched control subjects were prospectively and consecutively included. DED was diagnosed by the association of ocular symptoms and tear film abnormalities (Schirmer I test <5 mm/5 min and/or tear break-up test <10 s), with or without ocular surface damage (corneal and conjunctival staining), according to the DEWS criteria from the modified Delphi Panel Report.[4,13] Only the subjects with a best-corrected visual acuity of at least 0 logMAR were included, since this study focused on a decrease in visual function related to tear film degradation and ocular symptoms but not to extensive corneal damage. At inclusion time, all patients were treated with tear substitutes only, without any anti-inflammatory or cyclosporin medication, and without changes within the last 3 months. Healthy age- and sex-matched subjects with no ocular pathology, with no treatment, and without any symptoms or signs of DED (Schirmer I test >10 mm/5 min and Oxford score = 0) were included as controls. All participants were in good general health and were licensed drivers with at least weekly driving practice. Exclusion criteria were any ocular pathology but DED, eyelid malposition or dynamic disorders, previous ocular/eyelid surgery, contact lens wear, systemic disorder, pregnancy, and treatment changes within the last 3 months.

• CLINICAL EXAMINATION AND QUESTIONNAIRE: Slit-lamp evaluations were conducted in a defined sequence[14] and included tear break-up time measurement (s, mean of 3 consecutive tests), ocular surface fluorescein staining (grade 0-5, according to the Oxford score), lissamine green staining (grade 0-9, according to the van Bijsterveld score), and Schirmer I test (mm/5 min, without anesthesia). Before clinical examination, a trained interviewer (G.R.) administered the French version of the Ocular Surface Disease Index (OSDI) questionnaire, which was developed to quantify the specific impact of DED on vision-targeted health-related quality of life.[15] This disease-specific questionnaire includes 3 subscales: ocular symptoms (OSDI-symptoms), vision-related activities of daily living (OSDI-function), and environmental triggers. Each subscale (0-100) was computed, as well as an overall averaged score (0-100).

• DYNAMIC ABERROMETRY: Serial measurements of corneal and ocular wavefront aberrations were simultaneously performed every second for 10 s after blinking using the dynamic aberrometer KR-1 (Topcon, Clichy, France). The entire procedure has been previously described.[11] Briefly, HOAs were recorded in mesopic conditions without any pharmacologic mydriasis, analyzed by expanding the set of Zernike polynomials up to the sixth order, and expressed for the central 4-mm diameter. The progression index of total (third- to sixth-order) HOAs was defined as the slope of the linear regression line of HOAs throughout the recording period, as previously defined.[11]

• DRIVING TEST: We used a driving simulator purchased from Develter Innovation (Ile de France, France). This simulator has an automatic shift. Driving tests were performed with the best spectacle correction in scotopic conditions on a standardized 5-km circuit. Each test had a series of 7 lighted targets, increasing in intensity for 15 s and then disappearing. Lighted targets randomly appeared during the test at various positions and various driving conditions: straight forward, straight backward, at a crossroad entrance, and on the right-hand or left-hand side of a crossroad. For each target seen, the patient had to press a remote button on the wheel. Data included the number of targets seen/missed, their respective location, and the average response time. The results were determined as the mean of 3 consecutive tests.

• STATISTICAL ANALYSIS: All data are given as the mean ± SD. For ocular examinations—clinical evaluation, tear osmolarity measurement, and wavefront aberrometry—1 eye per patient was selected using a random number table in order not to bias the statistical relevance of the results. Data were controlled for normality, homogeneity of variances, and sphericity in order to perform the adequate tests. The 2 groups were compared using parametric *t* tests. In the DED group, scatterplots and Spearman correlation coefficients were used to assess the association between pairs of variables. The probability level of significance was adjusted according to the post hoc Bonferroni procedure in order to maintain an overall type I error equal to 0.05.

RESULTS

THE PROFILE, CLINICAL FEATURES, AND OSDI SCORES OF each group are detailed in the Table. Six patients presented

TABLE. Subject Profiles and Ocular Surface Disease Index Scores Between Dry Eye Patients and Age- and Sex-matched Controls

	Dry Eye Patients (n = 20), Mean ± SD (min/max [95% CI])	Controls (n = 20), Mean ± SD (min, max [95% CI])
Age (y)	53.4 ± 16.2 (22/84 [46.3-60.5])	53.1 ± 16.4 (22/84 [45.9-60.3])
Sex ratio (m/f)	0.25	0.25
Clinical data		
Tear break-up time (s)	5.9 ± 2.2 (2/10 [5.0-6.9])	11.4 ± 3.7 (4/15 [9.9-13.1])
Schirmer (mm)	9.5 ± 5.4 (1/20 [7.2-11.9])	19.6 ± 0.6 (15/20 [19.4-19.9]
Oxford (0-5)	1.1-0.8 (0-4 [0.7-1.4])	0
Van Bijsterveld (0-9)	2.7 ± 1.6 (0-6 [1.9-3.3])	0.1 ± 0.1 (0/1 [0-0.1])
Ocular Surface Disease Index		
Overall score	48.1 ± 18.4 (10.4/89.6 [40.6-56.6])	2.2 ± 2.9 (0/10.4 [0.9-3.3])
OSDI symptoms	43.3 ± 15.6 (15/80 [36.4-50.1])	2.1 ± 3.1 (0/15 [0.8-3.5])
OSDI functions	41.3 ± 27.8 (0/93.8 [29.1-53.4])	1.8 ± 2.9 (0/12.5 [0.5-3.1])
OSDI triggers	58.3 ± 29.2 (8.3/100 [45.6-71.1])	2.4 ± 3.9 (0/16.7 [0.7-4.1])

OSDI = Ocular Surface Disease Index.

mild-severity DED and 14 patients presented moderate-severity DED, according to the Delphi approach.[5] Significant differences in all the clinical characteristics and OSDI scores were found between DED patients and controls (paired t test, $P < .01$ for each).

• **COMPARATIVE ANALYSIS OF ABERRATION DYNAMICS BETWEEN GROUPS:** Significant variation with time in corneal total HOAs (repeated-measures ANOVA, $P < .01$), third-order coma ($P < .01$), and third-order trefoil ($P < .01$) was found in DED patients, whereas no significant change occurred in the control group throughout the recording period. As detailed in Figure 1, the progression index of corneal total HOAs and of corneal third-order trefoil was significantly higher in DED patients than in healthy controls ($P < .01$ and $P < .05$, respectively).

• **DRIVING VISUAL PERFORMANCE:** The average response time to identify targets was significantly higher in DED patients than in controls ($P < .01$) (Figure 2, Left). Moreover, a significant difference in the average number of targets seen was found between groups ($P < .01$), further depending on target location (Figure 2, Right): interestingly, targets appearing at a crossroad entrance and at the right-hand side of a crossroad were more often missed by DED patients than by healthy subjects ($P < .01$ and $P < .05$, respectively). On the contrary, targets appearing straight on (forward or backward) were equally detected in the 2 groups.

In DED patients, a positive correlation was found between the response time to identify targets and the progression index for corneal HOAs ($R^2 = 0.40$, $P < .01$) as well as between response time and the OSDI "symptoms" subscore ($R^2 = 0.25$, $P < .05$) (Figure 3). No significant correlation was found between the driving simulation data and the other computed data (Supplemental Table, available at AJO.com). Following a stepwise regression procedure, the response time was found to significantly depend on the progression index for corneal HOAs only (R^2 increment = 0.40, $P < .01$).

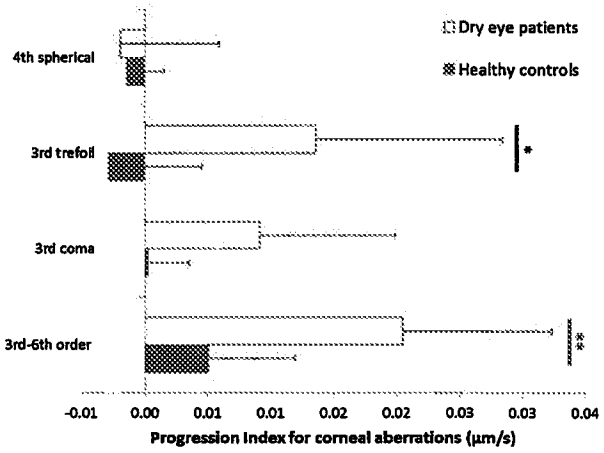

FIGURE 1. Comparative analysis of corneal aberration dynamics between dry eye patients and age- and sex-matched controls. Significant difference in the progression index for third- to sixth-order higher-order aberrations and for third-order trefoil between dry eye patients and controls (paired t test, *$P < .05$, **$P < .01$).

DISCUSSION

DED IS A CHRONIC OCULAR SURFACE DISEASE THAT affects millions of people worldwide.[1] The majority of patients with DED experience chronic ocular discomfort associated with impaired daily visual function and subsequent vision-related quality-of-life disturbance, further

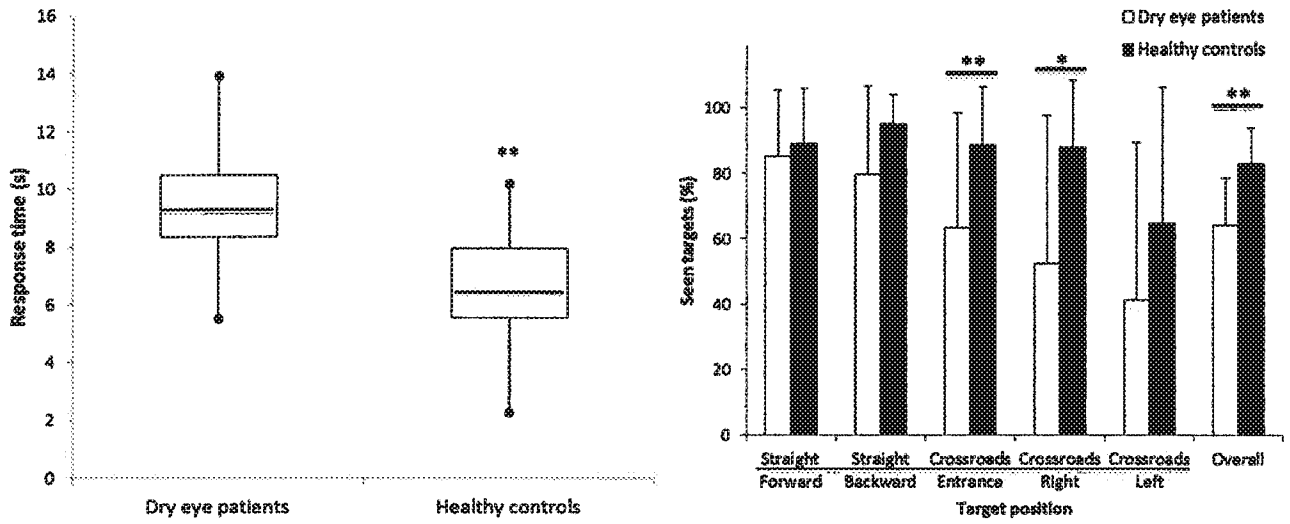

FIGURE 2. Comparative analysis of visual performance while driving between dry eye patients and age- and sex-matched controls. (Left) Average response time to identify targets in dry eye patients and in controls. Data are presented as median, 95% confidence interval, and range. (Right) Percentage of targets seen depending on target location (paired *t* test, $*P < .05$, $**P < .01$).

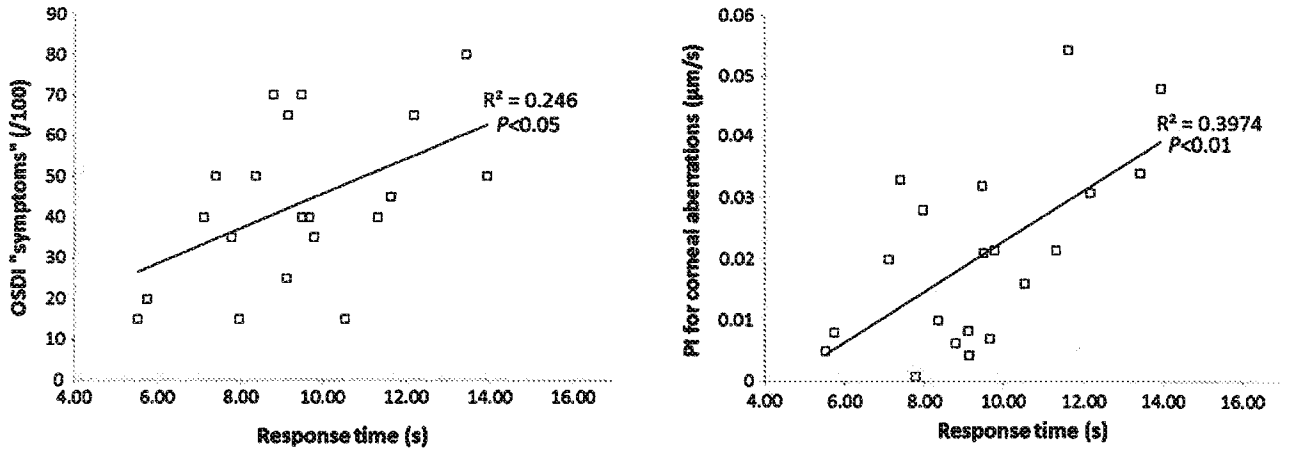

FIGURE 3. Linear relations between visual performance while driving and the other data in dry eye patients. Visual performance while driving, as assessed by the response time to identify targets during a driving simulation, was analyzed in correlation with the other data. (Left) Positive correlation between the response time and Ocular Surface Disease Index (OSDI) "symptoms" subscore (Spearman correlation test, $P < .05$). (Right) Positive correlation between the response time and progression index (PI) for corneal higher-order aberrations ($P < .01$).

impacting health status.[2] The present study objectively reports that the visual function is impaired during specific driving situations in DED patients as compared with healthy controls, further demonstrating that driving visual performance is correlated with ocular optical aberrations and patient-felt quality of life in this disease.

Tear film instability is reported to increase the progression with time of corneal HOAs after a blink.[16–18] The present study originally found a relation between tear film–related ocular optical degradation and driving difficulties. An increased blink rate is thought to compensate for corneal dryness, which stimulates tear secretion and creates a new tear film layer.[19] Goto and associates[19] found a deterioration of visual function during the fixation without blinking in 22 DED patients compared with 8 controls. The deterioration of vision after blinking supports the hypothesis that the tear film of patients with DED is unstable, especially when blinking is delayed. Precisely, we reported herein that DED patients missed more frequently targets at crossroad entrances than targets appearing straight on. We could hypothesize that this result is linked with a decrease in blink rate and subsequent increase in corneal HOAs when

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a specific driving situation requires more attention. Indeed, the elapsed time between blinks is known to increase in specific conditions, such as high driving speed.[19] In the present study, it could also have been interesting to record blink rate during the simulation to more precisely examine this point. Hence, other aspects of vision than standard visual acuity may be taken into account to better reflect the daily visual function, as clearly detailed by Owsley and McGwin.[20]

The association between loss of contrast sensitivity and driving disability has been previously studied on the one hand, and a decrease in contrast sensitivity has been reported in DED patients on the other hand. However, nothing was known about a direct link between DED-related contrast sensitivity impairments and driving difficulties. Although conventional contrast sensitivity testing was not performed in the present study, we reported a pronounced increase in response time in the DED group, which corresponds to the need for higher signal intensity to be perceived since the target contrast was increasing with time during a 15-second period. Rubin and associates studied the relationships between various indexes of visual function and driving ability in a population of 222 healthy volunteers.[21] The authors reported contrast sensitivity as the strongest correlating factor for subject-felt driving difficulty. Indeed, standard visual acuity, the most commonly used measure of visual function, does not correlate with some types of functional disability, such as driving.[21,22] Owsley and associates also reported that people with low contrast sensitivity have 8 times more road accidents than other people.[23,24] In dry eye, Rolando and associates compared 30 DED patients (18 patients with corneal damage and 12 without) with 15 healthy subjects.[22] They showed a significant decrease in contrast sensitivity in both DED groups as compared with controls. Interestingly, the authors confirmed that the quality of vision was reduced in DED whatever the visual acuity as standardly measured. In the present study, it could also have been interesting to perform conventional contrast testing, but our primary goal was to assess the visual performance in more realistic conditions. Our study confirms that visual impairments in patients with DED are not accurately evaluated by routine examination, further indicating the need for new visual criteria to better reflect visual function in daily living.

The subjective relationship between DED and driving difficulties has been previously described through the use of vision-related quality-of-life questionnaires.[12,25] Complementarily, our study is the first, to our knowledge, to objectively assess visual function in DED patients while driving, further establishing a direct link between DED, ocular optical degradation, and driving difficulties. Miljanovic and associates assessed vision-related quality of life with a questionnaire in a series of 190 DED patients vs 399 controls. They reported a decrease in driving ability in DED patients as compared with controls.[25] Herein several quantitative standardized measures of visual quality were correlated with patients' subjective perceptions, showing a significant correlation between the patient-reported OSDI symptoms score and visual difficulties during daytime driving as objectively assessed by a driving simulation. Difficulty in viewing lighted targets may be related to a disability in seeing or identifying external signals such as lights or traffic signs, but also pedestrians or other vehicles, when driving. Although subjects may have more difficulty while driving, it does not necessarily mean that they cannot drive safely. Future studies should evaluate the correlation with accidents rates. Such an approach could aid in developing efficient counseling for patients with DED and also in improving the driver's environment by providing, for example, high-contrast signs. The delayed reaction time found in DED patients could be linked with subject-felt discomfort when driving regularly, which could explain a feeling of insecurity and some loss of confidence in patients with ocular dryness. Since this feeling is reported to be enhanced when driving at night, it could be interesting to perform such a simulation in mesopic/scotopic conditions. Otherwise, a future study using artificial tears in driving conditions may aid in determining whether such a driving simulator could be useful in the evaluation of treatments.[26]

A current challenge for a physician in managing DED stems from the difficulty in making allowances for both objective clinical findings and patients' complaints in order to assist the patient as best as possible and optimize the therapeutic strategy. Today's lifestyle—which includes intensive daily visual activities, such as reading, driving, and using a computer/smart phone—requires excellent visual performance to achieve well-being. Our results better elucidate one of the reasons in which DED is responsible for a decrease in patient-perceived quality of life by establishing a direct link between DED, ocular optical degradations, and impairment in visual performance while driving. Hence we demonstrate that, beyond the conventional visual acuity measurement, specific ocular optical degradations related to DED may impact on daily living tasks, such as driving. We believe that such objective measures of visual performance could be relevant to better evaluate the severity of the disease and the impact of DED on this population's health status worldwide.

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EXHIBIT G

Utility Assessment among Patients with Dry Eye Disease

Rhett M. Schiffman, MD, MHSA,[1] John G. Walt, MBA,[1] Gordon Jacobsen, MS,[2] John J. Doyle, MPH,[3] Gary Lebovics, BA,[3] Walton Sumner, MD[4]

Purpose: To determine utilities (patient preferences) for dry eye disease.

Design: Survey study.

Participants: Fifty-six patients with mild, moderate, or severe dry eye treated by ophthalmologists in the Eye Care Services department of Henry Ford Health Care System.

Testing: Patients completed interactive software utility assessment questionnaires by the time trade-off (TTO) method. Utility scores were scaled such that a score of 1.0 = perfect health and 0 = death. Dry eye severity was independently classified using clinical parameters and physician/patient assessments. Global health status, visual functioning, and ocular symptoms were assessed by the Short Form-36 Health Survey, 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25), and Ocular Surface Disease Index survey instruments.

Main Outcome Measures: Utility scores for a range of dry eye severity states. These utilities were compared with utilities reported for other disease states. Correlations with the general and vision-related health status measures were conducted.

Results: Fifty-six patients completed the utility assessments with acceptable reliability. Mean utilities for moderate (0.78) and severe dry eye (0.72) by TTO were similar to historical reports for moderate (0.75) and more severe (class III/IV) angina (0.71), respectively. Utility scores correlated with the NEI VFQ-25 composite score ($\rho = 0.32$; $P = 0.037$) and with components of other health measures.

Conclusions: Utilities for the more severe forms of dry eye are in the range of conditions like class III/IV angina (0.71) that are widely recognized as lowering health utilities. Our results underscore how significantly dry eye impacts patients compared with other medical conditions. *Ophthalmology 2003;110:1412–1419 © 2003 by the American Academy of Ophthalmology.*

Dry eye disease is one of the most frequently encountered ocular morbidities, with as many as 4.3 million Americans older than age 65 with symptoms either often or all the time.[1] The dry eye syndrome is composed of a number of diverse medical and ocular diseases that involve decreased tear production and/or increased tear evaporation.[2] Because of the wide-ranging etiologies of dry eye and the great variability of clinical signs of the condition, it has been difficult to develop a consistent classification system for dry eye or reliable and valid measures of disease severity. This has complicated efforts to determine the incidence and prevalence of dry eye, to monitor disease progression and response to treatment, and to adequately quantify the impact that dry eye has on patients' quality of life. To this end, we have used several validated instruments to evaluate dry eye,[3] including the health-related Short Form-36 Health Survey (SF-36),[4] the vision-related quality-of-life measure NEI VFQ-25,[5] the Ocular Surface Disease Index (OSDI), and the Patient Perception of Ocular Symptoms.[3] Although nearly all of these measures yield a multidimensional profile of health status, none yields a single measure of how patients value various health states or outcomes.

Utility assessment is a formal method for quantifying patient preferences for health outcomes. For assessment at the societal or policy level, scale utility scores are typically anchored at perfect health (utility = 1) and death (utility = 0) and are measured on an interval scale.[6] Investigators might also assess clinical scale utility scores with less extreme anchors, such as the presence or absence of a condition of interest, for example, perfect vision (utility = 1) and blindness (utility = 0). The closer the utility value is to 1.0, the better the quality of life associated with that health state. Once utilities are scaled by use of comparable anchors, the impact of very different health states on quality of life can easily be compared.

Utilities can be measured in a number of ways. The time trade-off (TTO)[7] and standard gamble methods are the most

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widely used. Numerous researchers have concluded that patients most readily understand TTO.[8–11] Hence, the TTO method was used in this study. In TTO, the subject is offered two choices: (1) living t years, the life expectancy for a person in the current disease state followed by death, or (2) being in perfect health for fewer years ($x < t$) followed by death. The time in complete health, x, is varied until the subject is indifferent between the two choices. The utility weight is then x/t. A benefit of TTO compared with other utility tests is that it is more intuitive to patients while still capturing their risk preference. A limitation of TTO is that results might be biased upward, because subjects are asked to give up years at the end of life, which might be valued less.[11,12]

The purpose of this study was to measure utilities by TTO for the full severity range of dry eye states in a group of patients with dry eye and to determine how utilities correlate with disease severity and other health and vision quality-of-life measures. These utilities then could be used to compare patient preferences for dry eye disease outcomes with different symptomatic medical conditions, such as angina or blindness. They also could be used as weights in the calculation of quality-adjusted life years.[6] These quality-adjusted life years could be used as "denominators" in cost-utility analyses that allow health care policy makers to rigorously compare costs and health benefits across a wide range of medical interventions.

Material and Methods

Study Overview

Eligible participants completed several questionnaires between August 2000 and March 2001 to assess their sociodemographic status, general health status, visual functioning, and ocular symptoms. Next, they completed TTO utility assessments and underwent a detailed ophthalmic examination. Questionnaires and utility assessments were completed before the examination to ensure that the clinical encounter would not influence patients' responses. A convenience sample of patients returned 2 weeks later to complete the utility assessments a second time to determine test–retest reliability.

This study was conducted in compliance with the Code of Federal Regulations for sponsors and investigator obligations. Institutional review board/ethics committee approval was obtained. Written informed consent was obtained from all patients before enrollment.

Patient Selection

Patients were recruited if they were at least 18 years of age, had been diagnosed with dry eye (International Classification of Diseases, ninth revision = 375.15) at the Henry Ford Health System in the last 6 months and had symptoms for at least 3 months. Those scoring ≥8 on the OSDI were confirmed as symptomatic. A minimum score of 8 was chosen to ensure that all patients had at least mild symptoms, because a prior study found normal subjects to have an OSDI composite score of 4.5 ± 6.6 (mean ± standard deviation [SD]).[3] Participants had a life expectancy ≥1 year, corrected visual acuity of 20/40 or better in each eye, were English speaking, and were able to complete surveys without significant assistance. Those older than age 65 were screened with the Folstein mini-mental status examination questionnaire[13] to confirm that they were cognitively intact to participate in the study.

Exclusion criteria included uncontrolled systemic disease or disability affecting daily activities (such as ocular allergy, infection, irritation, or inflammation unrelated to dry eye disease). Also excluded were patients who had undergone ocular surgery (including cataract surgery) within the previous 6 months, who had undergone temporary or permanent punctal occlusion within the past 3 months, and those known to be allergic to any component of any study agent (e.g., lissamine green, fluorescein, or anesthetic).

Patient enrollment was prospective and consecutive from August 2000 to March 2001.

Main Outcome Measures

Utility Assessments for Dry Eye Disease. Utility assessments were made by means of the computerized interview U-titer software program (Computer Assisted Patient Education, Houston, TX), which provides a standard framework for measuring utilities,[14] taking into account patient life expectancy while permitting investigators the flexibility to program disease-specific scenarios for patients. U-titer has been used to measure utilities for psoriasis,[15] angina,[16] osteoporosis,[17] and prostate cancer.[18]

For the TTO utility assessments, patients reacted to a total of 9 scenarios or health states, including asymptomatic dry eye (requiring routine artificial tear use to completely avoid symptoms), mild dry eye (requiring only occasional treatment to treat periodic dry eye symptoms), moderate dry eye (requiring somewhat more frequent treatment for more persistent symptoms,) severe dry eye (requiring very frequent treatment for very severe symptoms), severe dry eye requiring tarsorrhaphy, monocular painful blindness, and binocular painful blindness. See Figure 1 for an example scenario and Figure 2 for a sample utility assessment question. Painful blindness was specified, because many symptomatic patients with dry eye perceive their dry eye symptoms as painful. Patients also assessed the utility of their current dry eye status. Finally, patients reacted to a scenario about their own comorbidities in the absence of dry eye. It is believed that patients can project what it would be like if they did not have the health condition being studied but had all other comorbidities.[7,16,19–21] As described later, this projection permitted us to estimate the utility for each of the health states in the absence of comorbidities.

Scaling of Utility Scores. TTO dry eye utility scores, which were reported on a scale with anchors of "death" and "perfect painless vision," were converted to a scale ranging from "death" to "perfect health." The latter scale is the traditional policy scale that permits comparisons with the broadest range of health states. This rescaling was conducted using the patients' own comorbidity utility score. The comorbidity utility score represents a subject's health were he or she to have all their current comorbidities but no dry eye. It represents the upper limit of what a patient's utility score could be before dry eye symptoms are taken into account. To rescale, the patient's utility score was multiplied by the reported comorbidity utility score to achieve a final utility score, which incorporates dry eye and all comorbidity and is scaled from "death" to "perfect health."[19]

Dry Eye–specific Utility Loss. If one fails to take comorbidity into account, it is possible to overestimate the lost utility because of the condition of interest and hence to overestimate the potential benefit of treatment.[19] To compute the magnitude of utility loss caused by dry eye alone, the patient's final utility score (comorbidity-adjusted dry eye utility score, the preference for having dry eye disease in the presence of associated comorbidities, on the "death" to "perfect health" scale) is subtracted from the patient's comorbidity utility score (the preference for being free of dry eye,

Severe Dry Eye

Imagine that your eyes feel dry, gritty or sore most or all of the time. Your vision is frequently blurred and fluctuates quite a bit. You use eye drops in both eyes every 1-2 hrs, but that provides only temporary and partial relief of your symptoms. You will use a lubricant at bedtime in both eyes. You will also undergo a painless 10-minute procedure in the doctor's office to block off the tear drainage system. There are no complications from this procedure.

Now imagine there's a treatment that would cure all of your symptoms of dry eye, including any vision problems you might have from dry eyes. You would no longer require any eye drops or any other medications for your dry eyes, nor would you require any procedures or surgeries for your eyes. This treatment, however, is accompanied by a reduction in your life expectancy (you will live a shorter life). Now, think about how much life expectancy you would be willing to trade in order to cure your symptoms of dry eye.

Figure 1. Sample scenario presented to patients undergoing the time trade-off utility assessment.

but still having all other comorbidities, also on the "death" to "perfect health" scale).

Additional Measures

Disease Severity. The severity of dry eye disease was rated by physician assessment and also by a composite disease severity score. The composite disease severity score, described previously,[3] is substantially less dependent on physicians' subjective assessments and is easily computed. It combines traditional clinical measures of dry eye (Schirmer's type-1 and ocular surface staining) with a symptom-based measure (patient perception of ocular symptoms) to evaluate dry eye in adherence with the recommendations of the National Eye Institute Workshop on Clinical Trials in Dry Eyes.[2]

Health Status Measures. General health-related quality-of-life was measured with the SF-36. Vision-related quality of life and ocular symptoms were assessed with the OSDI, the Patient's Perception of Ocular Symptoms, and the NEI VFQ-25. All surveys were completed by self-administration.

The SF-36 is a reliable, valid, and responsive measure of global health status that measures health status in 8 dimensions, including physical functioning, role limitation because of physical disability, bodily pain, general health, vitality, social functioning, emotional limitation because of emotional disability, and mental health. These measures are summarized by a physical component summary score and mental component summary score.[4]

The OSDI, developed by Allergan, Inc., is a reliable, valid, 12-item questionnaire designed to measure ocular disability from ocular surface disease (Drug Information J 1997;31:1436). The

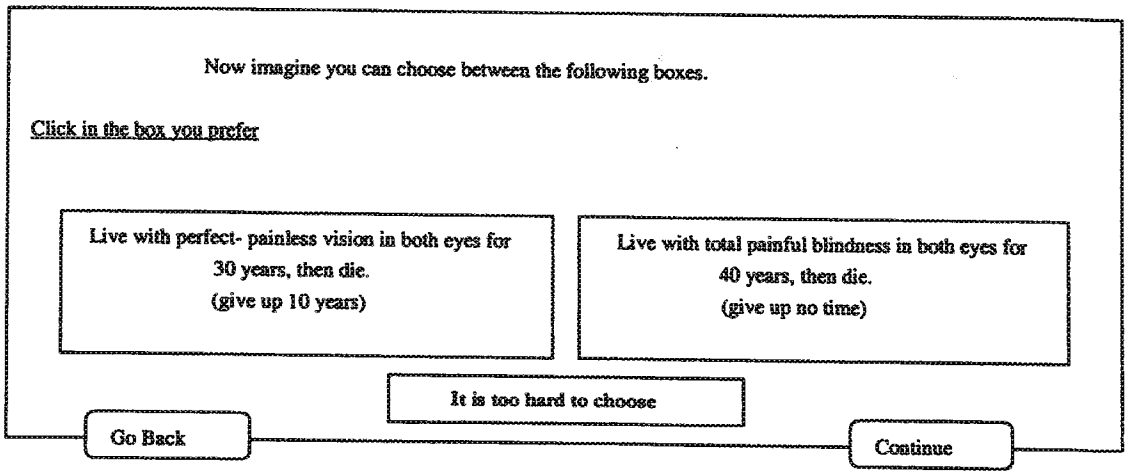

Figure 2. Sample question posed by U-titer in the time trade-off method of utility assessment. The number of years the patient has to consider is varied systematically until a point of indecision is reached. The initial number of years proposed to respondents depends on the demographic characteristics of the patient.

three subscales assess vision-related function, ocular symptoms, and environmental triggers.[3]

The Patient's Perception of Ocular Symptoms is a nine-level subjective facial expression scale used previously in dry eye studies[3] and is a component of the disease severity composite score.

The NEI VFQ-25 is a reliable 25-item questionnaire containing 12 scales: General Health, General Vision, Visual Pain, Near Vision, Distance Vision, Driving, Color Vision, Peripheral Vision, Vision-specific Social Functioning, Mental Health, Role Difficulties, and Dependency. It has been validated across a broad range of ocular disorders.[5]

Clinical and Sociodemographic Measures. Clinical measures included "walking-around" binocular Early Treatment of Diabetic Retinopathy Study visual acuity, ocular surface staining with fluorescein for the cornea and lissamine green for the conjunctiva (graded according to the Oxford scale), and tear production using Schirmer's test type-1 (without anesthesia). Sociodemographic data collected included age, race, gender, educational level, and household income.

Statistical Methods

Mean utility scores (± SD) were computed for all health states. To determine whether associations existed between patients' current dry eye utility and other health status measures, data were extracted from prospectively completed data forms, and Spearman correlation coefficients were computed. The κ statistic was used to evaluate agreement between patients and physicians regarding their assessments of disease severity. Finally, test–retest reliability was evaluated by computing intraclass correlations.

Statistical Power. The target sample size of 20 patients in each of mild, moderate, and severe dry eye groups (on the basis of physician assessment) was selected to detect an effect size of 0.4 for the utility scores, using a power of 0.80 and an α of 0.05. In this setting, an effect size of 0.4 corresponds to a difference between the largest and smallest group means that is approximately equal to the common standard deviation. Therefore, the chosen sample size yields adequate power to detect a mean group difference of 0.2, given an SD of approximately 0.2. This difference is clinically relevant; for example, mild angina has been shown to have a utility of 0.90, moderate angina 0.70, and severe angina 0.50.[22] For the total of 60 patients within each health state, a correlation coefficient of 0.36 would be detectable with a power of 0.80 (at an α level of 0.05).

Results

Study Population and Disposition

Fifty-seven patients with dry eye were enrolled. The mean age of this sample was 52.7 ± 13.9 years (range, 22–77). Eighty-one percent of patients were female. Sixty-one percent were white, and 39% were black. The mean number of years of education was 14.5 ± 2.8 (mean ± SD), and the mean yearly income was $49,000 ± $25,600 (mean ± SD).

Patients reporting higher utilities for binocular blindness than monocular blindness (indicating their preference for binocular blindness) or a higher utility for severe dry eye requiring surgery than for asymptomatic dry eye (indicating their preference for severe dry eye requiring surgery) were considered to have not understood the utility assessment process and were deemed interview failures. The interview failure (misordering rate) for the utility assessment was 29%. There were no significant predictors of interview failure as assessed by linear regression using sociodemographic factors (such as age and gender) as independent variables. Thus, assessments were based on 40 patients. Of the 40 patients, physicians classified 10 as having severe dry eye, 16 moderate dry eye, and 14 mild dry eye.

Table 1. Test-retest Reliability by Utility Assessment Method

	Time Trade-off (n = 11)	
Disease Severity Scenario	*Intraclass Correlation*	*P*
Asymptomatic dry eye	0.75	0.005
Mild dry eye	0.50	0.100
Moderate dry eye	0.43	0.161
Severe dry eye	0.73	0.007
Severe dry eye requiring surgery	0.31	0.323
Current dry eye	0.07	0.837

Study Validation

Test–retest Reliability. Overall, reliability was moderate to good for each of the dry eye states, as assessed by an analysis of test–retest reliability for a subset of patients (n = 11) who returned for a repeat utility assessment. Because of the modest sample size, only asymptomatic dry eye and severe dry eye scenarios were statistically significant (Table 1). The lowest test–retest reliability was seen for patients' self-assessment of their own condition ("current dry eye"), which was the only outcome that could theoretically change between test and retest.

Patient-physician Agreement in Designation of Dry Eye Severity. There was mild agreement between patients' self-assessment of disease severity and physician-assessed severity (κ = 0.39, 95% confidence interval, 0.18–0.61) and between self-assessed severity and disease severity composite score (κ = 0.33; 95% confidence interval, 0.13–0.52). For each disease severity, patients tended to grade their dry eye condition as less severe than that was assessed by the physician. This finding is not surprising considering that the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes concluded that subjective and clinical findings in dry eye patients do not correlate with each other.[2]

Utility Scores for Comorbidity, Blindness, and Dry Eye

Table 2 displays utility scores for comorbidity, blindness and for each dry eye severity grade. Blindness and dry eye scores are adjusted for comorbidity and scaled such that 0 = death and 1 = perfect health. Comorbidity is also scaled from death to perfect health.

For each dry eye state, utility scores ranged from 0.62 to 0.78. As expected, scores for the dry eye states made internal sense relative to the most extreme visual outcome assessed (binocular painful blindness). For example, utility for the most severe form of dry eye (requiring surgery) was 0.62 compared with 0.35 for binocular painful blindness. When patients were asked to rate their own current dry eye state, the mean utility score was the same as the mild dry eye utility score (0.81). However, the reported values ranged from 0.16 to 0.97.

Utility Loss Solely Attributable to Dry Eye

The lost utilities ("dysutility") caused by each blindness and dry eye state are presented in Table 3. As expected, there was modest condition-specific loss of utility for the mildest dry eye conditions (0.07), whereas the greatest loss of utility occurred with binocular blindness (0.52). Dry eye–specific utility loss because of the pa-

Table 2. Utility Assessments of Ocular Conditions and Comorbidities

	Time Trade-off Utility Score (n = 43)								
	Comorbidity in the Absence of Dry Eye	*Monocular Painful Blindness*	*Binocular Painful Blindness*	*Asymptomatic Dry Eye*	*Mild Dry Eye*	*Moderate Dry Eye*	*Severe Dry Eye*	*Severe Dry Eye Requiring Surgery*	*Current Dry Eye*
Mean	0.88	0.64	0.35	0.78	0.81	0.78	0.72	0.62	0.81
SD	0.14	0.29	0.31	0.23	0.18	0.19	0.23	0.26	0.19
Median	0.94	0.74	0.33	0.86	0.85	0.82	0.77	0.68	0.85

Scale: 0 = death to 1 = perfect health.
SD = standard deviation.

tients' current dry eye status (0.07) was on the average comparable to mild dry eye.

Association Between Current Dry Eye Utility Scores and Other Health Measures

In general, worsening utility scores for current dry eye correlated with worsening scores on the health status measures. The magnitude of correlation was generally mild. Unadjusted utilities for current dry eye correlated significantly with the ocular symptoms subscale of the OSDI, the bodily pain and role-emotional subscales of the SF-36, as well as the distance acuity and composite scores of the NEI VFQ (all $P \leq 0.048$) (Table 4). For adjusted utilities, significant associations were seen with the physical functioning, role physical, bodily pain, and vitality subscales, and the physical component summary score of the SF-36 (all $P \leq 0.045$), and also with the NEI VFQ composite score ($P = 0.037$).

Comparison of Utilities Between Dry Eye and Other Diseases

Table 5 compares our utility scores with other medical conditions reported on a scale of 0 = death to 1 = perfect health. Although all utilities listed were anchored on this policy scale, only some of these explicitly incorporated medical comorbidities as we have done. Those studies that explicitly reported comorbidity adjustments are denoted with asterisks in Table 5. Because of the possible differences in method, some caution should be exercised when making direct comparisons.

Mild dry eye requiring only intermittent treatment was the dry eye state resulting in the least dysutility (utility = 0.81). This level of dysutility is greater than that experienced by patients with mild psoriasis (utility = 0.89). The comorbidity-adjusted utility for moderate dry eye (0.78) was in the range of that reported for moderate angina (0.75), which was also comorbidity-adjusted. Severe dry eye and severe dry eye requiring tarsorrhaphy were associated with more dramatic reductions in utility (0.72 and 0.62, respectively). This is in the range of utilities reported by patients with class III/IV angina (comorbidity-adjusted utility = 0.71) and is worse than the utility for disabling hip fracture (0.65). Dry eye requiring tarsorrhaphy had even lower utility than monocular painful blindness (0.64). Conditions producing more dysutility than the most severe form of dry eye included moderate and major stroke, complete blindness, and AIDS. As a control, the utility calculated in this study for binocular painful blindness (0.35) was found to be similar to that seen in a previous study examining complete blindness (0.33).[23]

Discussion

To our knowledge, this is the first report of utilities for dry eye disease. We estimated the mean utility loss of severe dry eye in the absence of comorbidities to be 0.16 by the TTO method (Table 3). The interpretation of this lost utility is that patients expecting to live 10 more years would give up, on average, 1.6 years of that time to be rid of severe dry eye. This loss of utility is similar to that reported for moderate to severe (class III/IV) angina.[19] Less severe dry eye problems might carry a quality-of-life impact greater than that of mild chronic psoriasis. Even moderate dry eye yields comorbidity-adjusted utility scores and lost utility comparable to moderate angina (calculated from references 7 and 19. This suggests that effective treatments for dry eye disease can be expected to restore patient benefits of a magnitude comparable to the benefits produced by treatment for angina.

Numerous methods are available to measure utility. TTO

Table 3. Lost Utility Caused Solely by Ocular Condition

	Time Trade-off Lost Utility* (n = 43)							
	Monocular Painful Blindness	*Binocular Painful Blindness*	*Asymptomatic Dry Eye*	*Mild Dry Eye*	*Moderate Dry Eye*	*Severe Dry Eye*	*Severe Dry Eye Requiring Surgery*	*Current Dry Eye*
Mean	0.24	0.52	0.10	0.07	0.10	0.16	0.26	0.07
SD	0.22	0.29	0.16	0.07	0.10	0.14	0.20	0.07
Median	0.16	0.49	0.03	0.04	0.07	0.12	0.19	0.04

Scale: 0 = No lost utility; 1 = utility loss equivalent to the difference between perfect health and death.
*Lost utility = (Utility of comorbidities alone)-(Utility of ocular condition adjusted for comorbidities).

Table 4. Correlation of Unadjusted and Comorbidity-adjusted Current Dry Eye Utility Scores With Other Health Measures

	Time Trade-off (n = 43)			
	Unadjusted		*Adjusted*	
	ρ	P	ρ	P
OSDI				
Vision	−0.17	0.298	−0.14	0.377
Environmental triggers	−0.12	0.447	0.01	0.931
Ocular symptoms	−0.31	0.048*	−0.21	0.186
Total	−0.16	0.326	−0.08	0.632
SF-36				
Physical functioning	0.29	0.060	0.36	0.018*
Role limitation/physical	0.30	0.057	0.35	0.024*
Bodily pain	0.33	0.035*	0.32	0.037*
General health	0.16	0.310	0.15	0.348
Vitality	0.19	0.241	0.33	0.033*
Social functioning	0.27	0.084	0.26	0.103
Role-emotional	0.32	0.036*	0.24	0.125
Mental health	0.27	0.086	0.19	0.241
Physical component summary	0.30	0.056	0.31	0.045*
Mental component summary	0.27	0.084	0.16	0.315
NEI VFQ-25				
General health	0.12	0.453	0.25	0.112
General vision	0.16	0.327	0.21	0.173
Ocular pain	0.09	0.594	0.09	0.579
Near vision	0.24	0.122	0.24	0.127
Distance acuity	0.31	0.047*	0.25	0.110
Social functioning	0.17	0.273	0.19	0.232
Mental health	0.18	0.253	0.17	0.291
Role difficulties	0.28	0.078	0.30	0.056
Dependency	0.19	0.234	0.15	0.350
Driving	0.26	0.106	0.15	0.342
Color vision	0.22	0.166	0.28	0.070
Peripheral vision	0.02	0.922	0.24	0.130
NEI VFQ-25 composite	0.33	0.036*	0.32	0.037*

*$P \leq 0.05$.
OSDI = Ocular Surface Disease Index.

incorporates the quantity of life directly into the utility measure, which some believe makes this a preferred measure[24]; however, others have argued that, because the years given up are at the end of life, this could lead to an upward bias.[12] Perhaps the most important consideration is that comparisons across medical conditions should be made only using similar utility assessment methods and on similar scales.

TTO utilities had only modest correlations with the other health status measures. This was expected, because TTO requires patients to trade years of life, which depends in part on one's degree of risk aversion. The OSDI, NEI VFQ, and SF-36 require no such trade-offs and are not related to the respondent's risk tolerance. In general, unadjusted scores, which did not incorporate comorbidity, correlated better with the vision-related subscales, such as the ocular symptoms subscale of the OSDI and the distance acuity subscale of the NEI VFQ, whereas comorbidity-adjusted utility scores correlated better with global health status measures. Although current dry eye utility significantly correlated with NEI VFQ-25 composite score, the NEI VFQ-25 is not an adequate replacement for the TTO assay, because it is not a preference-based measure. Furthermore, the NEI VFQ-25 composite score is an unweighted average of the individual components and is not as theoretically valid as the TTO assay. Nonetheless, it is interesting to note that they correlate, underscoring how utility measures are important for measuring the way patients value their health state.

Several observations support the validity of our results. First, our utilities for monocular and binocular blindness are comparable with previously reported results.[9,23] Utilities for dry eye were acceptably reliable on the basis of test–retest intraclass correlations (the lowest reliability was seen for patients' self-assessment of their own condition, consistent with the fluctuations that patients with dry eye have with their symptoms). Moreover, the correlations of unadjusted and comorbidity-adjusted utility scores with other health status measures were in the expected direction for each health measure.

Although we specified "painful" blindness instead of blindness in our scenarios (because dry eye has painful symptoms), this did not result in any reduction in utility scores as might have been expected. It might be that our patients were more risk-averse compared with previously reported populations, or perhaps the marginal dysutility of "painful" in the presence of blindness was perceived as insignificant. Notwithstanding this, our utilities for blindness are strikingly similar to other reports.[9,23]

Some of our observations reflect the well-known complexity of utility assessment analysis and the multiple etiologies of dry eye disease. For example, our rate of misordered data was comparable to previous reports for utilities by TTO.[7] Although a high failure rate has the potential to bias the data, there were no significant predictors of failure rate in our analysis, indicating impartiality. The failure rate might have been lower had we used a selected patient group rather than consecutive enrollment. Also, physician-patient agreement on disease severity was weak, underscoring the differences between patient and physician perceptions of symptoms, and is consistent with the lack of correlation between dry eye symptoms and clinical signs.[2]

We did observe variability in dry eye utilities, as has been reported with utility assessments for other diseases.[7] As a result, it should be cautioned that our utilities might not apply to individual patients; however, from a societal prospective, these estimates (and particularly their trends) seem reasonable given the comparable results with previous reports for blindness.[9,23]

Increasing severity of dry eye from the asymptomatic dry eye to moderate dry eye range did not result in markedly lower mean utilities. For example, TTO utilities were higher for asymptomatic dry eye than for mild dry eye. However, the mean TTO utilities declined as the severity of dry eye increased across the entire spectrum of disease, consistent with our expectations.

Finally, although some analysts recommend assessing utilities from patients not affected with the medical condition of interest (to capture the societal perspective),[22] we desired to maximize the relevance of responses and therefore deliberately chose to sample patients with dry eye. This population also permitted us to correlate patients' utility

Table 5. Utility of Dry Eye Compared with Other Health States

Health State	Medical Condition of Subjects	Mean Utility Time Trade-off	Data Source
Treatment with warfarin	Atrial fibrillation	0.98	25
Mild psoriasis	Psoriasis	0.89	15
Mild dry eye*	Dry eye	0.81	This study
Asymptomatic dry eye*	Dry eye	0.78	This study
Moderate dry eye*	Dry eye	0.78	This study
Moderate angina*	Angina	0.75†	7, 19
Severe dry eye*	Dry eye	0.72	This study
Class III/IV angina*	Angina	0.71	19
Disabling hip fracture	Hip fracture	0.65	17
Monocular painful blindness*	Dry eye	0.64	This study
Severe dry eye with tarsorrhaphy*	Dry eye	0.62	This study
Moderate stroke	Atrial fibrillation	0.39	25
Binocular painful blindness*	Dry eye	0.35	This study
Complete blindness	Cataract	0.33	23
AIDS	HIV	0.21	26
Major stroke	Atrial fibrillation	0.11	25

*Comorbidity explicitly incorporated in utility.
†Calculated from data presented in both articles.

assessments with other clinical and vision-related quality-of-life measures among patients with the disease.

In summary, all severities of dry eye disease reduced quality of life, with severe dry eye resulting in lost utility comparable to that reported for moderate to severe (class III/IV) angina, underscoring the seriousness with which patients with dry eye view their disease. This substantial lost utility represents an opportunity for therapeutic interventions, and these results provide the basis for rigorous cost-effectiveness analyses for dry eye disease.

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EXHIBIT H

THE 2002 GALLUP STUDY OF DRY EYE SUFFERERS

Summary Volume

- Eight in ten dry eye sufferers (79%) agree that if left untreated, dry eye can lead to more serious eye problems. Despite this widespread agreement, six in ten (61%) say they don't treat their dry eye as regularly as they should.

- Three in four (74%) wish there was a more effective treatment for their dry eye, yet nearly as many (69%) say they are satisfied with the treatment being used. However, it should be noted that almost twice as many strongly agree that they wish there was something more effective than are satisfied with the current treatment (34% vs. 19%).

- A majority of sufferers take their dry eye problem seriously as only one in three (35%) agree *"dry eyes are no big deal"*.

- Fewer than four in ten (36%) feel their dry eye problem might be a symptom of another health problem.

The Question: *Please indicate the extent to which you agree or disagree with each of the following statements. (Q. 30)*

ATTITUDES TOWARD DRY EYE

	Agree Strongly %	Agree Somewhat %	Disagree Somewhat %	Disagree Strongly %	Don't Know %	Total %
You can never be too careful when it comes to eye health.	73	22	4	0	1	100
If left untreated, dry eye can lead to more serious eye problems.	31	48	18	2	1	100
I wish there was something more effective to treat my dry eye.	34	40	19	5	2	100
I am satisfied with the dry eye treatment I am using.	19	50	21	8	2	100
Dry eyes are an inevitable part of aging.	14	53	26	6	1	100
I don't treat my dry eye as regularly as I should.	13	48	23	14	2	100
I am worried my dry eye is a symptom of another health problem.	10	26	37	25	2	100
Dry eyes are no big deal.	6	29	32	31	2	100

(n=501)

IMPORTANCE OF ATTRIBUTES IN BRAND PURCHASE DECISION

- A doctor's recommendation (85%) is the attribute most likely to be rated very important in the brand purchase decision of eye ointment or gel. Majorities also assign very important ratings to a product that is long-lasting (73%) or fast-acting (66%).

- Substantially smaller proportions rate as very important the brand reputation (40%) or price (31%).

	Users of Ointment/Gel					
	Very Important	Somewhat Important	Not Very Important	Not At All Important	Don't Know	Total
	%	%	%	%	%	%
Physician recommended	85	5	1	5	4	100
Long-lasting	73	14	2	2	9	100
Fast-acting	66	17	4	2	11	100
Brand reputation	40	23	12	10	15	100
Price	31	23	32	1	13	100

(n=47)*

* *Sample size too small for reliable statistical analysis.*

The Question: *How important are the following attributes in your decision of what brand of eye ointment or gel to purchase? (Q. 29)*

EXHIBIT I

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A UNIFIED THEORY OF THE ROLE OF THE OCULAR SURFACE IN DRY EYE

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1. INTRODUCTION

Dry eye symptoms arise from a series of etiologies and are manifest in different patients with varying severity. The National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes, under the chairmanship of Dr. Michael A. Lemp, defined specific subtypes of dry eye in order to standardize clinical tests used in diagnosis and design of clinical studies.[1] The use of artificial tears is palliative at best, resulting in a reduction of ocular surface eyelid shear forces and some symptomatic relief. Future research should focus on mechanistic endpoints. What causative factor(s) initiates the sequence of events resulting in the clinical symptoms suffered by the patient?

This review emphasizes observations that the ocular surface (cornea, conjunctiva, accessory lacrimal glands, and meibomian glands), the main lacrimal gland, and the interconnecting reflexive innervation compose a "functional unit" (Fig. 1) whose parts act together as a servomechanism and not in isolation. In the normal individual, when afferent nerves of the ocular surface are stimulated, a reflex results in immediate blinking, withdrawal of the head, and secretion of copious amounts of reflex tears from the main lacrimal gland. These tears contain proteins, mucin, and water. Similarly, in people who face chronic ocular surface irritation due to environmental factors (contact lens, low humidity, wind, etc.), there is chronic stimulation of the lacrimal gland resulting in secretion of "sup-

Lacrimal Gland, Tear Film, and Dry Eye Syndromes 2
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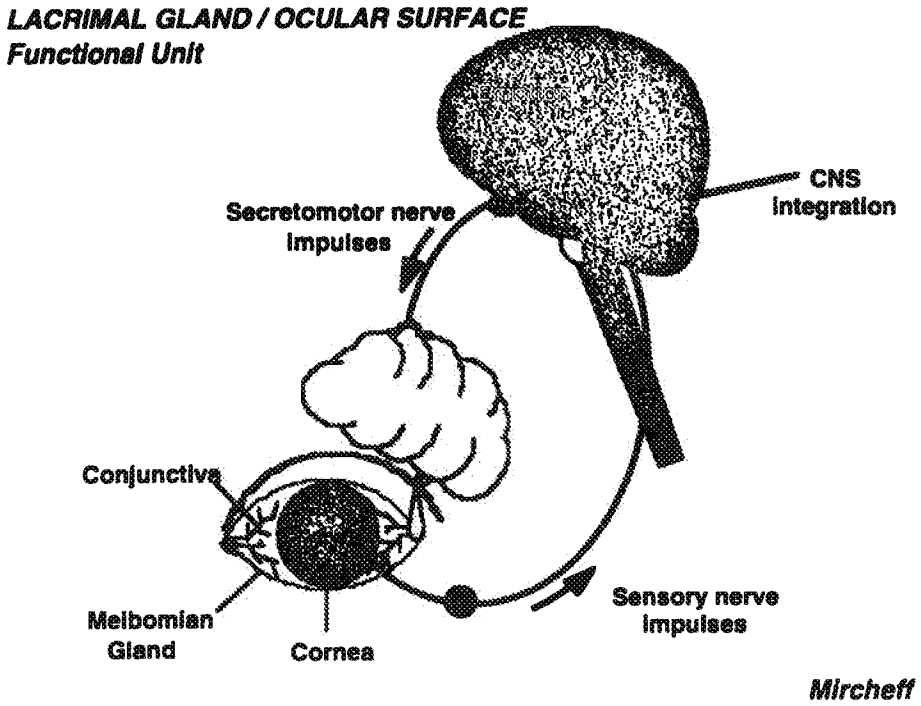

Figure 1. The functional unit comprising the ocular surface, the main lacrimal gland, and the interconnecting innervation.

portive" tears that can maintain and repair the ocular surface. In individuals suffering from dry eye, however, chronic inflammation of the ocular surface as well as of the lacrimal glands can be detected.

This "chronic" inflammation results in inflammatory cytokine secretion from the main lacrimal gland as well as the ocular surface that may interrupt both afferent and efferent arcs of the reflex and therefore impair function. The result of this pathology is a constant ocular surface irritation, which in its most severe form propagates a debilitating disease progression resulting in an inability of the patient to function normally at home or in the workplace.

The alterations in each component of the ocular surface/lacrimal gland reflex will be described.

2. OCULAR SURFACE

The ocular surface is challenged by the shear force across its surface due to blinking,[2] air currents, low humidity-induced desiccation, and foreign bodies (including contact lenses). Additionally, the ocular surface is confronted with several types of bacteria as well as viruses. The ocular surface in normal individuals remains intact and is able to repair the damage produced by these constant insults. Pflugfelder et al.[3] have shown, that diagnostic dyes, rose bengal and fluorescein, do not stain normal conjunctiva or cornea. Nelson et al.,[4] using impression cytology, however have indicated that some transient ab-

normalities can be found in clinically normal conjunctiva of people living in challenging environments. Patients with Sjögren's syndrome, who demonstrate a severe lack of aqueous tears, stain abundantly in the exposure zone.[4] In normal individuals, minor traumas, such as those already described, are rapidly healed and pose no chronic threat to the ocular surface. This is possibly due to the presence of a trophic surface environment consisting of a normal, non-inflammatory tear film. The tears in the normal individual may vary in quantity. It appears that a chronic alteration in nerve stimulation of the lacrimal gland in a dry eye individual results in inflammation and lymphocytic infiltration of the lacrimal glands. This results in secretion of diminished and altered tears that contain inflammatory cytokines, resulting in an abnormal ocular surface epithelium. The conjunctival and corneal epithelia have also been demonstrated to be competent to secrete IL-1α, TNF-α, IL-6, and IL-8.[5] The question then becomes, what conditions result in the inability of the ocular surface and the lacrimal glands to respond normally to chronic environmental challenges? Although this has not been resolved, several studies have indicated that a dramatic loss in systemic androgens found in a major target population, the peri- and post-menopausal female, results in a loss of support for lacrimal secretory function and production of an anti-inflammatory environment.[6,7]

3. CONJUNCTIVA

The conjunctiva covers the entire ocular surface outside of the cornea. Its surface is composed of a stratified mucus-secreting epithelium and a population of goblet cells also responsible for the mucus secretion. Mucus is one of the main defense mechanisms against various microtrauma. Shear forces applied during blinking (12–15/min) can cause significant trauma to the non-lubricated ocular surface.[2] If superficial trauma is induced by placing a Schirmer test strip or impression cytology membrane on the conjunctival surface, the eye will stain with rose bengal. In the normal eye, staining will no longer be observed after 24 h, indicating that a reparative process actively restores the normal surface barrier. Pflugfelder et al. (personal communications) have developed a model of conjunctival responses to microtrauma in the rabbit using nitrocellulose membranes to remove the superficial two cell layers. Then healing and cellular wound healing behavior are followed. An increase in epithelial proliferation was detected within 1 h and remained elevated for 3 days. Abnormal patterns of expression of various cell markers were detected for 1 week. A marker for basal epithelial cells, cytokeratin 14, was expressed throughout the entire epithelium,[8] and the number of cells staining for the presence of conjunctival mucin was reduced.[9] Increases in the concentrations of mRNA for inflammatory cytokines such as TNF-α, IL1-α, and IL-8 were also detected within conjunctival epithelial cells at the site of the microtrauma.[10] This phenomenon is important in part because of the conjunctival squamous metaplasia seen in moderate to severe dry eye as well as in Sjögren's syndrome. This response is seen as chronic wound healing due to the constant motion of the upper eyelid shear forces generated during blinking. Cytokine synthesis is then initiated in the traumatized corneal and conjunctival epithelium, as well as cytokines present in the lacrimal secretions, in an individual with an unsupported ocular surface (Fig. 1). In Sjögren's syndrome patients, T-cell infiltration of the conjunctiva has been found in both the epithelium and stroma.[11,12] Increased levels of IL-1α, TNF-α, IL-6, IL-8, and IL-10 have been found in the conjunctival epithelium of these patients when compared to control.[5,13] These patients, for the most part, also demonstrated expression of immune activation markers HLA-DR and ICAM-1.[5] The immunomodulatory drug cyclosporine,[13] as well as steroids,

have been found to reduce ocular surface rose bengal staining. Additionally, studies in the dry eye dog model have demonstrated that cyclosporine A eliminates both the conjunctival and lacrimal gland lymphocytic infiltrates. [4]

Alterations in the conjunctiva, such as those mentioned, occur as increased tear film abnormalities in people with keratoconjunctivitis sicca (KCS). A chronic inflammatory environment on the ocular surface results in pathologic alterations of the conjunctival epithelium known as squamous metaplasia.[3,15] A decrease in tear fluid secretion has been correlated with an increase in conjunctival rose bengal staining.[4] Patients with Sjögren's syndrome, who are unable to tear even in response to stimulation of the nasal mucosa,[16] have very severe ocular surface irritation. Patients with a decrease in lacrimation also have a decrease in various proteins such as lactoferrin and lysozyme.[17,18] Several other proteins, secreted in tears, that may be trophic to the ocular surface as well as providing an anti-inflammatory environment, are also being investigated.[13,17] It is reasonable to assume that in situations where these proteins are diminished, a pathogenic environment will exist in the ocular surface.

In many types of dry eye, in particular those associated with systemic signs of autoimmune disease, the lacrimal gland becomes infiltrated with lymphocytes. These inflammatory cells adversely affect the function of the lacrimal gland, resulting in altered tear composition and compromise of the ocular surface. The initial glandular dysfunction, however, is most probably caused by a "disconnect" at the neural/glandular interface in the perivascular region. Interruption of the neural signal at this juncture is probably part of the same mechanism that initiates the migration and proliferation of lymphocytes in the lacrimal gland and conjunctiva.

4. OCULAR SURFACE INNERVATION

The ocular surface is exquisitely innervated, with the cornea having a density of free nerve endings approximately 60X that of tooth pulp. Corneal sensation is very acute and is centrally processed and interpreted solely as pain. The conjunctiva does not transmit as acute sensations as does the cornea and is known to feel itch as well as some temperature discrimination. It is well known that corneal stimulation results in a rapid reflex including immediate blinking, profuse reflex tearing, and withdrawal of the head. The neural pathway for this reflex as well as normal tearing have been partially elucidated (Fig. 2). Sensory (afferent) traffic from the cornea and conjunctiva travels down the ophthalmic branch (1) of the trigeminal nerve (V) through the trigeminal ganglion into the spinal trigeminal nucleus located in the brainstem. The initial synapse occurs in this nucleus, and neurons then travel up to the midbrain (pons), or the preganglionic sympathetic neurons in the spinal cord and then the superior cervical ganglion, located in the paravertebral sympathetic chain. Efferent fibers from the pons extend, via the facial (VII) nerve, to the pterygopalatine ganglion located adjacent to the orbit, where they again synapse and then send fibers to the lacrimal gland where they influence the secretomotor function (modulation of water and protein transport). Sympathetic fibers from the superior cervical ganglion also enter the lacrimal gland. Schafer et al.[19] have indicated that parasympathetic neural transmission can be inhibited by cytokines. Therefore, the pro-inflammatory cytokines such as are found in the lacrimal and salivary gland biopsies of patients with Sjögren's syndrome may inhibit neural stimulation of these target tissues.

It is important to note that the control of accessory lacrimal glandular secretion as well as conjunctival goblet cell secretion is only now being investigated. Work by Seiffert

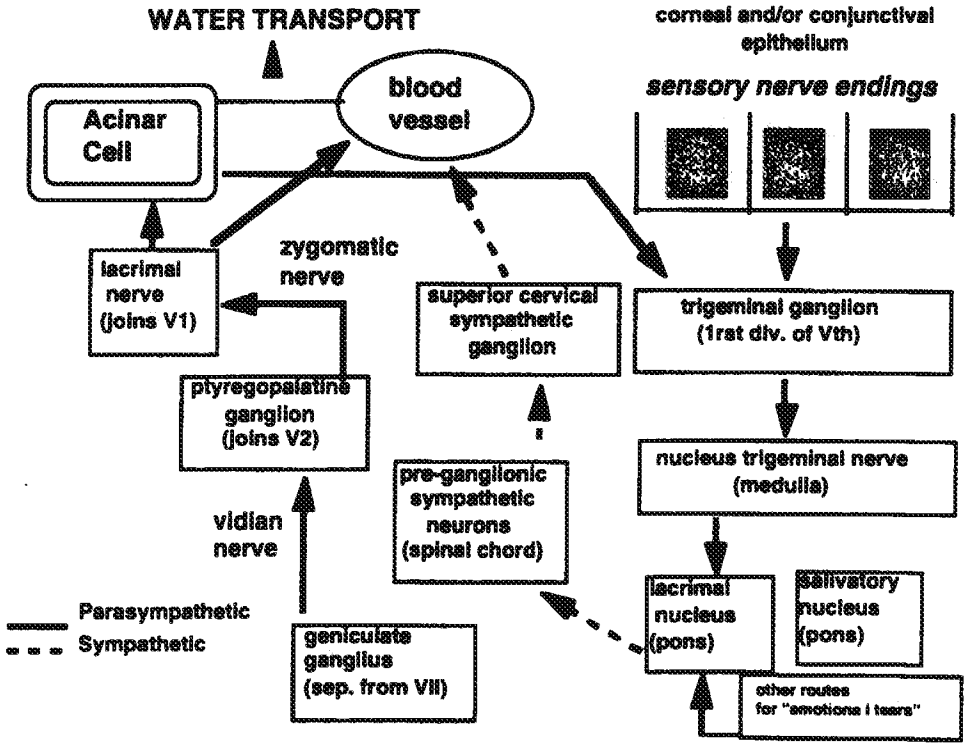

Figure 2. Afferent and efferent paths of lacrimal gland innervation for stimulation of tear flow.

et al.,[20] has demonstrated that the accessory glands are innervated, and Dartt et al.,[21] have also shown that the conjunctival goblet cells are innervated and respond to the presence of vasoactive intestinal peptide (VIP).

5. LACRIMAL GLAND

The lacrimal glands sit at the other end of the neural reflex. The main lacrimal gland resides just superior and temporal to the ocular globe. The accessory glands of Wolfring and Krause reside with the superior bulbar conjunctiva and the upper lid respectively. Although the etiology of dry eye is believed to be multifactorial and can be related to deficiencies in any of the three layers of the tear film, the major cause in Sjögren's syndrome has been reported to be a deficiency in aqueous tear production from the main and accessory lacrimal glands.[1,7] As in the salivary glands of patients with Sjögren's syndrome, as well as the conjunctiva in dogs with KCS,[14] the lacrimal glands of patients with immune-related dry eye have been found to be progressively infiltrated with lymphocytes. Immunohistochemical studies have demonstrated that these infiltrates consist primarily of CD4+ T cells and B cells.[22,23] Classically, this type of lymphocytic accumulation in the interstitium of the lacrimal or salivary gland is thought to result in immune-associated destruction of the epithelial cells in the target tissues, reduce aqueous tear secretion, and subsequently cause dry eye. The possible mechanisms are currently under investigation and discussion. The accumulated evidence indicates that the epithelial cells in the lacrimal and salivary

tissues have the potential to be antigen-presenting cells. In vitro, the lacrimal acinar cells have shown the ability to express MHC II following carbachol induction.[24] In vivo, acinar cells in the salivary gland of patients and the lacrimal gland of MRL/lpr mouse model of Sjögren's syndrome strongly express class II antigens.[5,25,26] Additionally, a recent study using PCR-single-strand conformation polymorphism (SSCP) showed that some infiltrating T cells in both lacrimal and salivary glands of Sjögren's patients recognize the shared epitopes on autoantigens, suggesting the importance of restricted epitopes of common autoantigens in the initiation of Sjögren's syndrome.[27] Therefore, it is reasonable to propose that the epithelial cells in inflamed lacrimal or salivary tissues are able to present autoantigens to the cell surface receptors such as T cell antigen receptors. The activated T cells can then secrete inflammatory cytokines such as IL-1β, IL-2, IFN-γ, and TNF-α, which may contribute to a continued local autoimmune stimulation and result in infiltration and proliferation of migrating T-cells within the glands, which, left unchecked, would result in glandular destruction.[28–30] Additionally, these pro-inflammatory cytokines can inhibit neural transmission of parasympathetic pathways and subsequently suppress neural stimulation of the lacrimal gland.[19]

It has become clear that lacrimal gland function is significantly influenced by sex hormones.[31,32] Among these actions discovered during the past decade, androgen has been found to exert essential and specific effects on maintaining the normal glandular function as well as suppressing the inflammation in the lacrimal gland of normal and autoimmune animal models.[32–37] This unique capacity of androgens is initiated through its specific binding to receptors in the acinar nuclei of the lacrimal gland and, in turn, lead to an altered expression of various cytokines and proto-oncogenes in these lacrimal gland epithelial cells.[7,38] The immmunosuppressive activity of androgens in lacrimal gland during Sjögren's syndrome is proposed to be attributed to its ability to induce the accumulation of anti-inflammatory cytokines such as TGF-β.[7,39] Given the critical role that androgen plays in many aspects of lacrimal gland, from anatomy to molecular modulation, it has been hypothesized that a decrease in androgen level below a certain threshold may result in lacrimal atrophy.[6] Apoptosis in the plasma cells of the lacrimal gland interstitium was detected 4 h following withdrawal of androgen in ovariectomized rabbits with atrophic and necrotic changes in the acinar cells occurring over the ensuing several days.[37] The resulting apoptotic fragments are also suggested to be a source of potential autoantigens and could be subsequently presented either by interstitial antigen-presenting cells or acinar cells to CD4 cell antigen receptors to initiate the autoimmune response. Our recent study in KCS dogs indicated that apoptosis plays an important role in dry eye pathogenesis. The data suggest that both the elevated epithelial cell apoptosis and the suppressed lymphocytic apoptosis in the lacrimal and conjunctival tissues of KCS dogs may be involved in the dry eye mechanisms.[40]

6. SUMMARY

It is our belief that the pathology of dry eye occurs when systemic androgen levels fall below the threshold necessary for support of secretory function and generation of an anti-inflammatory environment (Fig. 3). When this occurs, both the lacrimal gland and the ocular surface become irritated and inflamed, and they secrete cytokines that interfere with the normal neural connections that drive the tearing reflex. This leaves the lacrimal gland in an isolated condition, perhaps exacerbating atrophic alterations of the glandular tissue. These changes allow for antigen presentation at the surface of the lacrimal acinar

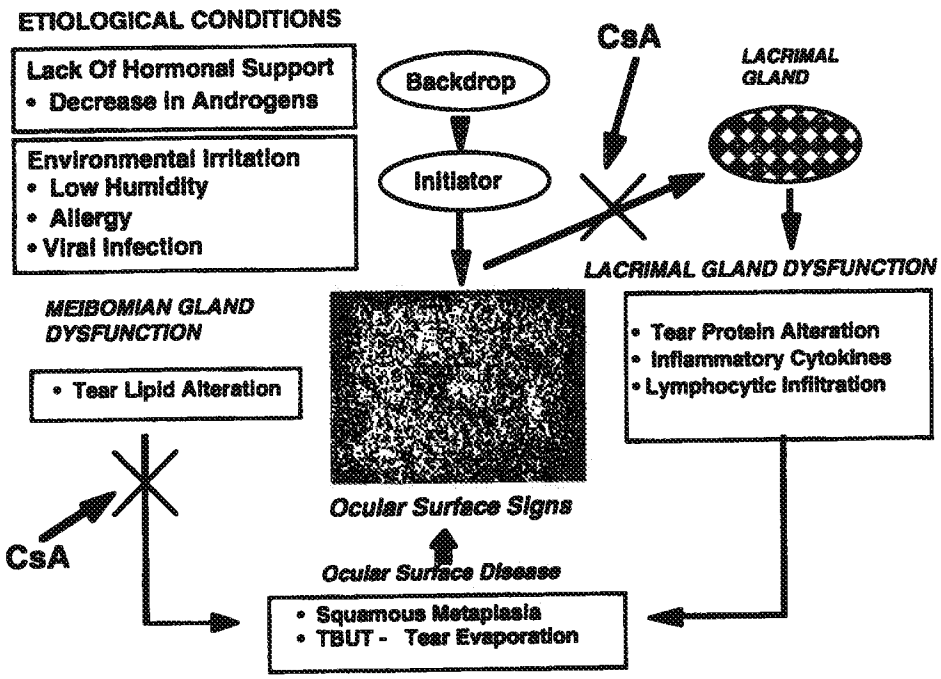

Figure 3. Proposed model of etiology and pathogenesis of dry eye. Included are etiologic factors (background, initiator) and the sequence of events resulting in alterations of the ocular surface. Possible therapeutic interventions (cyclosporine, androgens) are indicated.

cells and increase lymphocytic infiltration of the gland. A similar series of events may be occurring on the ocular surface.

From this hypothesis we conclude:

1. The ocular surface, lacrimal gland, and interconnecting innervation act as an integrated servo-mechanism.
2. Once the lacrimal gland loses its androgen support, it is subject to immune/ neurally mediated dysfunction.
3. The ocular surface is an appropriate target for dry eye therapeutics.

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EXHIBIT J

Integrating Restasis into the Management of Dry Eye

Stephen C. Pflugfelder, MD

The approval of cyclosporin emulsion for treatment of the inflammatory component of dry eye by the US Food and Drug Administration in December 2002 represents a major paradigm shift in the treatment of dry eye and in our understanding of its pathogenesis. There is mounting evidence from basic and clinical research demonstrating that inflammation is both a cause and consequence of dry eye. Certain inflammatory mediators, such as interleukin 1 have been found to cause lacrimal dysfunction though functional paralysis of the secretory epithelia,[1] whereas others (eg, interferon-γ and tumor necrosis factor-α) may interfere with normal differentiation and promote apoptosis of lacrimal gland and ocular surface epithelial cells.[2,3]

Topical cyclosporine emulsion has been found to have a salutary effect on ocular irritation symptoms, tear production, and ocular surface epithelial disease in patients with keratoconjunctivitis sicca.[4] Several mechanisms of action of cyclosporine emulsion have been identified, including inhibition of epithelial apoptosis and cytokine production by the activated T lymphocytes that infiltrate the conjunctiva in keratoconjunctivitis sicca.[5,6] T-cell infiltration of the conjunctiva has been found to be a feature of Sjögren and non-Sjögren syndrome keratoconjunctivitis sicca.[7] These T cells seem to be chemoattracted by the stressed ocular surface epithelia and once in place produce factors such as IFN-γ that push differentiation of the ocular surface epithelium toward a poorly wettable skinlike pattern. These findings suggest that keratoconjunctivitis sicca is similar to psoriasis and inflammatory bowel disease, conditions where T cells have been identified to play a key role in the epithelial pathology.[8,9] The improved understanding of the pathogenesis of keratoconjunctivitis sicca, particularly the role of T cells in this process, helps to explain the observed clinical efficacy of topical cyclosporine emulsion for treatment of this condition.

How does cyclosporine emulsion fit into the armamentarium for treatment of keratoconjunctivitis sicca? An international task force held at the Wilmer Eye Institute in December 2003 proposed a treatment algorithm for treatment of dry eye based on scientific evidence and clinical experience.[10] This group categorized dry eye into 4 severity levels based on irritation symptoms, clinical signs, and diagnostic tests. Patients with level 1 severity complain of mild episodic irritation symptoms, may have an unstable tear film, mild conjunctival dye staining and no corneal epithelial disease. In level 2, patients now experience chronic irritation symptoms and show evidence of peripheral corneal epithelial disease. In level 3, the central cornea is involved and patients may develop filamentary keratitis and level 4 is blinding dry eye, such as severe Sjögren syndrome or Stevens-Johnson syndrome where the cornea may opacify or ulcerate. Therapy of level 1 disease consisted of artificial tears, elimination of offending environmental factors, or systemic medications increasing oral intake of omega-3 fatty acids. The addition of cyclosporine emulsion to these other therapies was recommended for treatment of level 2 and worse disease where the chronic nature of the disease and ocular surface epithelial changes indicates an inflammatory component. There was consensus among the group that ocular surface inflammation should be controlled before temporary or permanent punctual occlusion.

The improved understanding of the role of inflammation in the pathogenesis of dry eye raises the issue of whether cyclosporine therapy should be initiated prophylactically in patients who are at high risk for developing level 2 severity or worse disease, such as patients with Stevens-Johnson syndrome, systemic autoimmune conditions (eg, rheumatoid arthritis and systemic lupus erythematosis) or early signs of graft-versus-host disease after allogenic bone marrow transplant.[11] Early intervention may minimize the risks of developing debilitating irritation and blinding complications such as permanent goblet cell loss, stem cell deficiency, or corneal ulceration that can develop in these diseases. Additional evidence will be required to address this issue.

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EXHIBIT K

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OSN EXCLUSIVES

COVER STORY

Panel recommends treating ocular surface prior to any refractive procedure

Eighty-six percent of patients with dry eye have both meibomian gland dysfunction and aqueous deficiency, an important consideration when optimizing the corneal surface before surgery — any type of ophthalmic surgery.

Whether PRK, LASIK or cataract surgery is the scheduled procedure, the greatest risk factor for a poor outcome in refractive surgery is pre-existing dry eye, according to **Eric D. Donnenfeld, MD**, who chaired the OSN New York Dry Eye, Anti-inflammatory and Allergy Corneal Health Roundtable.

"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery, including cataract surgery," Donnenfeld said. "We can improve the outcomes dramatically by managing these patients."

OSN New York Corneal Health roundtable participants tackle the issues of treating aqueous deficiency as well as meibomian gland dysfunction, giving their own twists on current recommendations. Crossing specialty lines, a glaucoma specialist adds his thoughts on advances in medical management of glaucoma that trend toward minimizing the effect on the ocular surface.

Cover story starts on page 10

Marguerite B. McDonald, MD, FACS, is among authors who have published studies on the utility of a preoperative course of cyclosporine.

Retained subretinal perfluorocarbon more prevalent with smaller-gauge vitrectomy

A higher incidence of retained perfluorocarbon was found in patients who underwent 23-gauge vitrectomy rather than traditional 20-gauge repair of retinal detachment.

"After transitioning from traditional 20-gauge vitrectomy to 23-gauge vitrectomy, it appeared to me that there was an increased incidence of subretinal perfluorocarbon liquid," **Sunir J. Garg, MD**, said.

Garg retrospectively reviewed 234 retinal detachment repairs he had done over a 3-year period and found a 10.3% incidence of retained PFCL when he used the smaller-gauge instrumentation. Incidence was 2.3% in the 20-gauge cases.

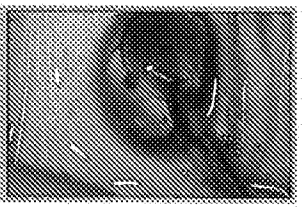
"Although microincision vitrectomy is a great advance, with any new technology comes subtle changes that we might not appreciate or realize," Garg said. "I expected there might be a slightly higher rate of subretinal PFCL with 23-gauge vitrectomy, but not a 4.5-fold increase."

Reducing turbulence within the eye is the critical part of primary surgery. Garg has begun using valved 23-gauge cannulas, which create less turbulence, he said.

Two other options for decreasing turbulence are reducing the infusion pressure when using non-valved cannulas and clamping the infusion line when removing instruments from the eye.

A follow-up study using valved 23-gauge cannulas is currently under way.

For more on this story, see page 9.



COVER STORY

Panel recommends treating ocular surface prior to any refractive procedure

The biggest risk factor for a poor outcome in refractive surgery is pre-existing dry eye, according to a panel of experts.

"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery, including cataract surgery," **Eric D. Donnenfeld, MD**, OSN Cornea/External Disease Board Member, said at a panel gathered to address management of ocular surface disease. Patients who are being evaluated for LASIK and PRK overwhelmingly have preoperative dry eye, he said.

"We can improve the outcomes dramatically by managing these patients," Donnenfeld said at OSN New York during the Dry Eye, Anti-inflammatory and Allergy Corneal Health Round Table, which he chaired.

Getting started

Donnenfeld kicked off the discussion with the case of a 43-year-old myopic woman with mild to moderate dry eye. The edited round table follows; the panelists discussed off-label use of some products.

Donnenfeld: In a myopic patient with active staining of the conjunctiva and cornea and with mild to moderate dry eye, what is the best refractive procedure? Many ophthalmologists would say PRK, and others would say no treatment, as would be expected, but there are additional options.

Douglas A. Katsev, MD: If the patient is 43 years old, it is hard to put in a phakic IOL. PRK, in my experience, causes less dry eye than LASIK, but certainly maximizing the tear film and treating with all appropriate medications and heat to the lids is the most important thing to do before getting started in any direction.

Donnenfeld: How common is it to have mixed mechanism disease, that is, both meibomian gland dysfunction (MGD) and aqueous deficiency, and how would you treat it?

Marguerite B. McDonald, MD, FACS: Michael Lemp published a paper proving that 86% of the patients with dry eye have concomitant MGD.

Donnenfeld: So this is the rule. In the past, we treated one or the other. We need to think about treating both of these diseases to maximize results. Let's start by talking about aqueous-deficient dry eye. What would be your starting point for managing this patient?

Treating aqueous deficiency

Henry D. Perry, MD: I would start with non-preserved artificial tears and topical cyclosporine, which is sometimes underused in patients with mild dry eye disease. It is important in any type of chronic ocular surface disease, especially due to aqueous deficiency, to begin topical cyclosporine.

Donnenfeld: What if the patient does not want to wait 3 to 6 months for cyclosporine to hit full stride?

Perry: Then we also have nutritional supplements. Fish oil, especially omega-3, is helpful, and we can see results in as little as 2 weeks.

Donnenfeld: I like nutritional supplements as well. In our practice, we use second-generation omega-3 fish oils in which the natural triglyceride provides significantly greater DHA and EPA absorption than first-generation fish oils that have been converted with alcohol to an ethyl ester form. I believe brands such as Nordic Natural in stores and PRN in doctors' offices, which is what I use, provide much better results.

In addition, we have been adding topical corticosteroids such as loteprednol when we initiate therapy. Combination immunomodulation does great work to get these patients comfortable, and it reduces burning and stinging.

McDonald: Some experts have recommended a run of topical steroids first and then starting Restasis (cyclosporine ophthalmic emulsion 0.05%, Allergan). I start patients on both simultaneously, largely because when patients have steroids first, they never want to start cyclosporine. They do anything they can to stay on the topical steroids, which do two things: They blunt or totally eliminate the stinging that often accompanies the induction of cyclosporine therapy, and they give immediate symptomatic relief. So patients have real belief that your suggested regimen is working. And in 4 to 6 weeks, you can turn this person from a suboptimal candidate for laser surgery into a pretty good candidate.

Donnenfeld: That is the key here. You need to evaluate these patients, and if they respond, they become good candidates for LASIK or PRK. If they do not respond, then you are probably best off doing nothing. There is a new steroid that will be coming out that I think is going to be exciting for this type of case, and that is loteprednol gel, which will be available in the first quarter of 2013. I think that will provide even more ocular surface coverage and better contact time.

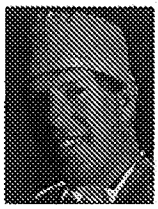
Perry: In our office, when we start topical cyclosporine, we always start a low-dose corticosteroid. Several authors have shown the efficacy of increasing the success of topical cyclosporine with low-dose loteprednol, and it has been shown by two other groups that the concomitant use of steroids is beneficial, not only in the initial treatment, but also in allowing the success of the long-term use of topical cyclosporine.

Katsev: When you are going to start cyclosporine, patients need to know that they are going to be taking this medication for 4 to 6 months. They need to communicate to me that they are willing to take it that much. I also start topical steroids, so I need commitment for 4 to 6 months and

Round table participants

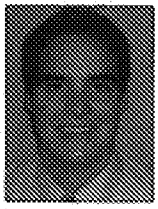

Eric D. Donnenfeld
Moderator


Richard M. Awdeh


Douglas A. Katsev


Kenneth R. Kenyon


Marguerite B. McDonald


Robert J. Noecker


Henry D. Perry

I need to know that they understand the disease.

McDonald: With loteprednol etabonate starting at the same time as cyclosporine, I prescribe four times a day for 2 weeks, twice a day for 2 weeks, and then the patient is off the loteprednol while the cyclosporine continues.

Donnenfeld: That is the Asclepius Panel recommendation.

Kenneth R. Kenyon, MD: I continue to believe that it is important to definitively diagnose aqueous-deficient dry eye by determining if the patient, in fact, has aqueous deficiency. Back in the day, we performed basic secretion Schirmer tests with topical anesthetic. Three decades later, I continue to use this same test to screen for aqueous deficiency. The notion that a patient with a basic secretion Schirmer score of perhaps 10 mm in 5 minutes has an aqueous-deficient dry eye and therefore deserves Restasis and/or punctum occlusion is simply incorrect. In such a case, other mechanisms of ocular surface disease, such as MGD, exposure or decreased corneal sensation, must be investigated.

I am sure we all have our differing views, but I will say that it is important to be clear when you are doing a pre-laser vision correction workup to have space on your diagnostic forms for both lids and tear functions. It will keep you out of trouble; it will keep you out of malpractice suits. I am certainly concurrent with everything else that has been offered about various medical and pharmaceutical therapies, but a Schirmer test tells me a heck of a lot and then allows me to decide whether to go down the route of plugs or even punctum cauterization, which after the inflammatory component of the surface is under control, is a time-honored valid therapy.

Donnenfeld: Punctal plugs work fairly well in aqueous-deficient dry eye. You want to stabilize the ocular surface first. If you want to make a patient unhappy, in my experience, put a punctal plug in someone with significant MGD. Those patients are just miserable. So, when do you start punctal plugs in these patients?

Kenyon: I have become cognizant of the notion that you do not want to create an ocular surface cesspool, as it were, by totally denying all aqueous and, hence, other toxic waste outflow. But after you get the surface in good anti-inflammatory status, then it is time to intervene with punctum occlusion, whether by a homemade "quick and dirty" 3-mm length of 5-0 chromic suture or with more extended duration intracanalicular inserts such as Oasis or semi-permanent silicone plugs. These are all variations on the theme. But first it is anti-inflammatory and then it is punctal occlusion, if you, in fact, have a true aqueous-deficient component.

Anti-inflammatories in glaucoma

Donnenfeld: Do you find that anti-inflammatory therapy, notably cyclosporine, plays a role in glaucoma management?

Robert J. Noecker, MD, MBA: Without a doubt. When you look at the demographic information, these are two diseases with parallel comorbidities. In the general population, a rough statistic for ocular surface disease in age-matched controls is around 15% vs. around 50% in the glaucoma population. The argument is that glaucoma therapy tends to make people worse.

Donnenfeld: A lot of glaucoma specialists resist the idea of early surgery, but for the corneal specialist, often the best thing to do is to get the patient off the glaucoma drops. Often, I will recommend something simple, like laser trabeculectomy or selective laser trabeculoplasty in phakic patients or an iStent (Glaukos) if the patient is having cataract surgery, to get a patient off of a glaucoma medication.

Noecker: Certainly SLT and laser interventions are easier to do. And now we have microinvasive glaucoma surgeries, which are lowering the bar in terms of not causing significant morbidity commonly associated with glaucoma surgery.

The other point is that it is an amazing time in glaucoma medical therapy because there are so many options to avoid the common preservative we talk about: benzalkonium chloride (BAK). If it is not possible from a formulary standpoint to eliminate BAK, then every new formulation has less and less BAK than the formulation had 5 or 10 years ago. You can have people on a preservative-free prostaglandin or a non-BAK alternative preservative prostaglandin. You can have them on preservative-free dorzolamide timolol. You can have them on preservative-free timolol alone. You can have alternatively preserved brimonidine. So you could do a whole treatment regimen without ever having to worry about the preservative effect. Active ingredients certainly and pH also play a role, but the preservative is the common denominator.

Donnenfeld: As a corneal specialist, if you can get patients off of these drops for a lifetime, the quality of life and the improved vision are significant.

Meibomian mechanism

Donnenfeld: Because we are talking about a mixed mechanism of ocular surface disease, let's move on to the management of MGD. What would be your first line of therapy for managing someone with MGD?

Cover story continues on page 12

POINT / COUNTER

With the emphasis on optimizing the ocular surface and minimizing preop dry eye, what is the value of the Schirmer test in particular before conducting refractive surgery?

POINT

Popularity of Schirmer test eroding


Thomas John

Ocular surface optimization should be considered an integral part and package of current day refractive surgery in order to deliver the optimal visual outcome, meet our patients' high expectations, and convert them to satisfied customers. In this endeavor there are various venues to pursue with regard to pre-refractive surgery detection of dry eyes, and one age-old test is the Schirmer test. Since its entry into this arena, Schirmer test rapidly gained popularity among clinicians, primarily driven by the fact that it is readily available, is relatively inexpensive, is easy to perform, and lacks clinically noticeable side effects. However, like everything else in life, its sustained popularity as an aqueous tear deficiency test has been slowly eroding, as reflected by one of the ASCRS surveys that reported 70% of the surgeons are not using pre-refractive surgery Schirmer test.

So why is there a change of heart toward Schirmer test? It is multifactorial, and some of the reasons may be attributed to the fact that the results can be quite variable. Based on the Schirmer test, one report showed that 17% of asymptomatic subjects would be misdiagnosed as dry eye patients. A more recent study showed that subclinical tear deficiency indicated by low Schirmer test values did not influence PRK outcomes in patients matched by age and magnitude of refractive correction.

It is important to listen to patient symptoms of dry eye, look for clinical biomicroscopic signs of dry eyes even in those asymptomatic individuals, and consider incorporating some of the newer, technology-driven dry eye tests that may be suitable in your refractive surgery practice.

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***Thomas John, MD,** is an OSN Cornea/External Disease Board Member. Disclosure: John has no relevant financial disclosures.*

COUNTER

Schirmer test still relevant


Penny Asbell

Dry eye continues to be a significant problem and a cause of dissatisfaction after laser surgery. There are a lot of reasons why these patients might have dry eyes, but the key reason is preop dry eye disease. So when we are thinking about laser, we should be thinking about preop diagnosis of dry eye disease. In a study that asked physicians what they do to evaluate patients before refractive surgery, as expected nearly 100% of physicians said they perform corneal topography, but only 30% of the physicians performed Schirmer's. We may argue that Schirmer's isn't the best dry eye test; nonetheless it is interesting to see that the physicians were not thinking about that. That's a take-home message. Let's think about it before the laser, not afterward.

Excerpted from Asbell PA, Gadaria N, Lee K-I. "The Ocular Surface and its Impact on LASIK and PRK" presented at OSN New York, Nov. 16-18, 2012.

Reference:
Solomon KD, et al. *J Cataract Refract Surg.* 2002;28(2):346-355.

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Cover story continued from page 11

Perry: The first thing is be sure of the diagnosis, as Dr. Kenyon said. I like to express the glands to get a feeling for the consistency and where we are in terms of the MGD in that particular patient. Heat is essential to melt the fats to get them flowing, and it is important that we remember that in this particular disease the change from long-chain fatty acids to free fatty acids with the inflammation leads to saponification or a soap formation. The problem is that there is too much detergent in the tears. Artificial tears can do a lot to help, and topical cyclosporine, topical steroids and nutritional supplements are also helpful. Lid hyperthermia is essential. Oral doxycycline changes the equilibrium constant from free fatty acids back to long-chain fatty acids and helps decrease the inflammation, as does topical azithromycin. Pulsed light therapy also helps in terms of heating, but there have been some disasters that occurred when the iris was fried by mistake.

Donnenfeld: I have become a big believer in nutritional supplements. What do you recommend to your patients who have MGD?

Richard M. Awdeh, MD: The increased importance of nutritional supplements is clear, both to us as a society and to us in clinic and with our patients. I will recommend that patients go on a vitamin therapy or TheraTears (Akorn) type of nutritional supplement, but additionally I ask patients to review their diet for rich foods — chocolates, cheeses, wines, caffeine, nuts — and I will ask them to modify their diet.

For these patients, I do not like putting them on an oral systemic therapy unless we get to that point, and if we do, then we will put them on oral doxycycline 100 mg two times per day for a few weeks and then switch to 100 mg daily. We ask them to take it with a snack and avoid sun exposure and ambient sun.

We have had success with topical azithromycin, again doing a staged approach, starting a low-dose steroid and then tapering the steroid down as the azithromycin has time to work.

With topical cyclosporine, there are instances when patients are not comfortable with it. We have a compounding pharmacy that creates the topical cyclosporine in different concentrations and in different vehicles, including a corn oil, for instance. We sometimes notice a good response in patients who were previously intolerant.

Kenyon: Half of my blepharitis and meibomitis patients do well simply with a warm compress for 5 minutes and erythromycin. That is traditional. Another 25% with any hint of rosacea will be knocked off with low-dose doxycycline or minocycline, which can go on benignly for years. So all this is good stuff, including LipiFlow (TearScience), but there is still a lot out there in the traditional armamentarium.

> **"We have taken a new approach of evaluating patients for ocular surface disease before considering any type of surgery."**
> — ERIC D. DONNENFELD, MD

LipiFlow expression

Donnenfeld: Consider the case of a 55-year-old patient with a long history of tired eyes, no medications, no corneal or conjunctival staining, drinks heavily, 2+ MGD, shortened tear break-up time who is treated with hot compresses, nutrition and LipiFlow. Patients who have marginally compensated ocular surfaces respond by blinking more often, and when they blink more often, they develop tired eyes. He had the therapy, the tired eyes got better, and the blinking reduced.

Kenyon: I have no proprietary interest here, but one of my practice partners, Jack V. Greiner, MD, has been doing studies for TearScience, so I have watched developments with interest. I believe LipiFlow works, but it is pricey.

Having said that, Greiner has done follow-up studies on some of his patients for more than 2 years, and this single 12-minute pulsed heat therapy does indeed unblock the glands. Whether it is by the subjective surveys such as the Ocular Surface Disease Index and the Standard Patient Evaluation of Eye Dryness, or all the objective measures, LipiFlow therapy does seem to have a protracted effect. So despite the self-pay "sticker shock" disadvantage, you can at least reassure patients that they will benefit for at least a year or perhaps longer.

McDonald: When we do hot compresses at home, most of that heat is wicked away by the lid structures, which are highly vascular. So little of the externally applied heat gets all the way back to where we want it to — the meibomian glands. But with the LipiFlow system, the heat is applied from the tarsal plate conjunctival side of the lid, so that the altered meibum becomes liquefied; then gentle pulsations start and the altered meibum is extruded. It is a much more effective way to apply heat, and to a much higher temperature — though still to a controlled and comfortable degree — than patients could ever get at home.

Tears and optimizing the surface for surgery

Donnenfeld: Consider the same patient who is going to have LASIK or PRK who had mixed mechanism ocular surface disease and is now better. Let's talk about what can be done surgically.

Literature now shows that making thin planar flaps gives better results. Bevel and side cuts provide better adhesion. Flaps can be smaller. In the old days, we were making 9.5-mm flaps for myopes. In a patient with a small pupil, you can go down to 8.1- or 8-mm flaps. You have half the surface area; half the corneal nerves are cut. There are a lot of ways for surgical modification. I do not think personally that there is now a big difference between PRK and small-flap LASIK with advanced techniques. In the old days when we made 150-µm flaps there was a big difference, but now I think PRK and LASIK are both reasonable techniques for managing these patients.

Awdeh: I agree. The key is to get the patient to baseline before surgery and to make sure that their symptoms have improved. Make sure that your objective is such that the patient is also true to the Schirmer's test and staining of the cornea.

Donnenfeld: Dr. McDonald, you wrote one of the definitive articles on using cyclosporine in these patients. How long do you continue cyclosporine after LASIK, and does it really affect the visual results?

McDonald: Yes. There are now at least five papers in the peer-reviewed literature documenting that whether you are old or young, male or female, and dry or not, you will have a better post-LASIK clinical outcome with a preop run-in of cyclosporine and using it for at least 3 months afterward. One of those papers is ours, using cyclosporine in extremely dry eye patients, who are considered very high-risk LASIK candidates. It made a big difference in the percentage of patients who achieved 20/20 uncorrected vision and in the percentage that needed an enhancement, both in favor of the cyclosporine-treated group.

Kenyon: Based on your work, I use Restasis for at least a month preop in any patient with a Schirmer test value of less than 5 mm basic secretion. I can continue it for up to 3 months postop. I always do LASIK in these patients because I think that their ocular surface is less compromised from the beginning, so the neurotrophic component of creating a LASIK flap is far offset by the need for the epithelium to regenerate in a potentially drier environment. If you do everything that we have described here to optimize the ocular surface first, then you will not get into trouble later with ocular surface difficulties, whether due to a single mechanism or a combined mechanism.

Donnenfeld: Ed Manche just published a paper in *Ophthalmology*, in which LASIK was done in one eye and PRK in the other eye, and patient healing was evaluated. There was no difference in dry eye between the two groups, and the healing was better in the LASIK group because of the problems of epithelial remodeling.

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EXHIBIT L

Article Date: 9/1/2013

Focus on Dry Eye

Restasis: 10 years after launch

The drug has found a strong niche in dry eye therapy.

By Jerry Helzner, Senior Editor

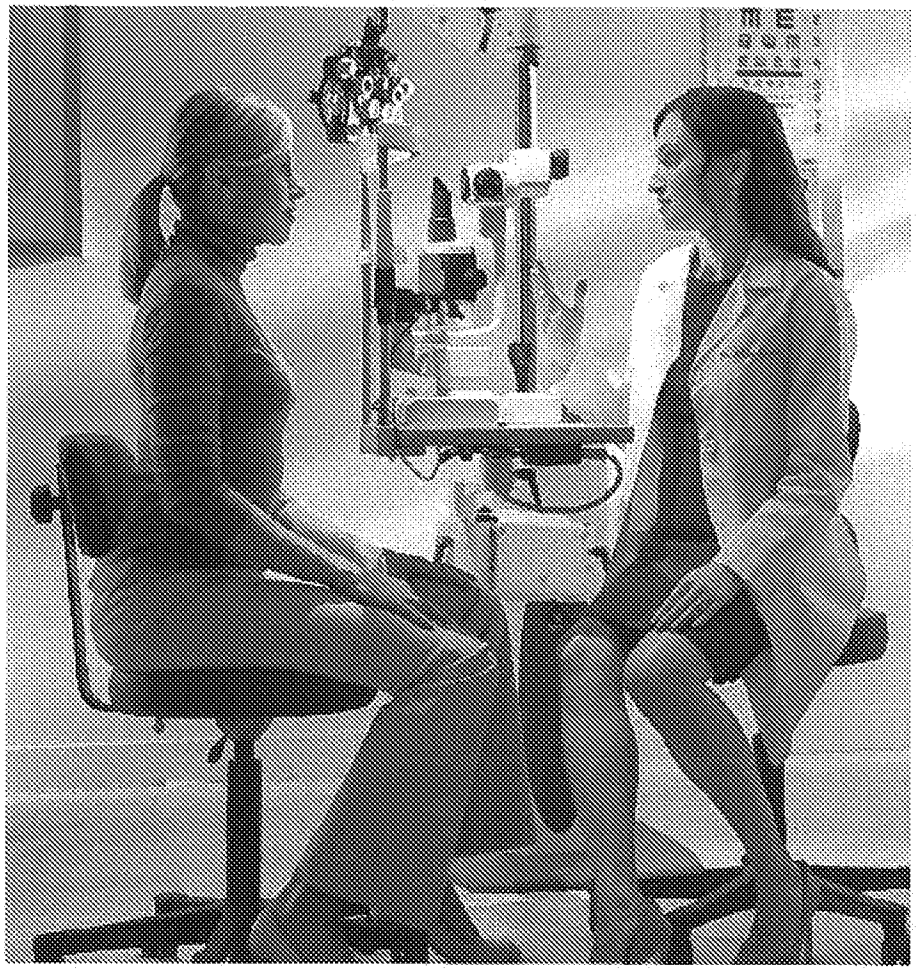
Launched by Allergan in the United States in April 2003, Restasis (cyclosporine ophthalmic emulsion 0.05%) had the advantage of being the first — and still the only — FDA-approved prescription drug for chronic dry eye disease. For people who had spent years trying to cope with their disease, primarily with oceans of artificial tears, just two drops of Restasis each day was designed to attack the underlying inflammatory characteristic of the disease and allow patients to produce more natural tears.

Sales continue strong growth

Now, a decade after it was introduced, Restasis can be deemed a success. Ophthalmologists interviewed for this article say it has earned a significant place in their overall treatment plan for combating dry eye disease. Patients worldwide have now accounted for 16 million prescriptions for the drug, translating to a compounded 40% annual sales growth, according to Allergan. In 2004, its first full year of US sales, Restasis totaled $98 million in revenues. This year, Allergan expects Restasis to record between $870 and $900 million in worldwide sales, making it the company's best-selling ophthalmic drug by far.

In the latest reported quarter, the second quarter 2013, Restasis was still growing sales by double-digits (10.5%), even though the drug has been in the marketplace for a decade. What's more, Restasis has been blessed with an ongoing marketing campaign featuring a series of television ads that focus on the endorsement of cornea specialist Alison Tendler, MD, of Vance Thompson Vision in Sioux Falls, S.D.

Given that Restasis has made a considerable impact on the treatment of dry eye disease over the past 10 years, what have ophthalmologists who treat dry eye learned about the drug during this time that allows them to use it more effectively? This article will focus on the experiences of three corneal specialists who have successfully integrated Restasis into their arsenal of dry eye treatments, two of whom actually use Restasis themselves.



A scene from one of a series of Restasis television ads featuring spokesperson Allson Tendler, MD.

THE LEARNING CURVE
Restasis needs time to work

Stephen Pflugfelder, MD, of the Cullen Eye Institute at Baylor College of Medicine in Houston, has extensive experience with Restasis, having served as an investigator in the drug's pivotal phase 3 trial. He believes Restasis came along at just the right time. "In terms of treating dry eye and ocular surface disease, prior to the introduction of Restasis, artificial tears just weren't cutting it because inflammation is a big part of the disease," he says. "Restasis has helped us to treat the inflammation."

Dr. Pflugfelder says he went through a learning curve in the use of Restasis that has helped him to be more accurate in selecting patients for whom the drug is most effective. "First, it's very important for both doctors and patients to recognize that it takes a while for Restasis to begin to work," he notes. "It could be four to six weeks and it could even be longer, but I have found that the drug's effectiveness gets better with time. It is so safe that you can use it indefinitely, which is a major advantage."

Dr. Pflugfelder says patients who produce low tear volume at baseline tend to do better on Restasis than patients who produce more of their own tears. He has also conducted in-house research that points to patients with low goblet cells as good responders to Restasis therapy. "Restasis appears to have the ability to repair goblet cells," he notes.

Can Allergan fight off generic Restasis?

If imitation is the sincerest form of flattery, than Allergan should feel quite flattered these days. As the basic patent for Restasis is set to expire in May 2014, generic drug manufacturers are salivating at the chance to get into the marketplace

with their version of what is now close to a $1-billion-a-year drug.

A generic version of Restasis may be close at hand if recent FDA draft guidance becomes a reality. In June, the federal agency proposed that human trials of generic Restasis may not be necessary if laboratory testing can demonstrate the chemical equivalence of the drugs. With that standard for approval, the timetable for a generic version could be pushed ahead by years. That fact was not lost on Allergan stockholders as the price of Allergan shares tumbled 12% the day after the FDA draft guidance was announced.

Allergan has already begun the fight to ensure that human trials are conducted for any generic version of Restasis. In a statement issued following the FDA announcement, Allergan said it believes the FDA's proposed testing method "cannot predict clinical safety and efficacy, and thus cannot be used to establish bioequivalence."

Allergan said it will provide feedback to the FDA during the 60-day comment period. The company asserts it is weighing all options in an effort to prove the FDA's proposal, if carried out, would not be in the best interests of consumers.

Two factors could work in Allergan's favor to forestall competition. First, the Restasis manufacturing process is highly complex and could delay a potential competitor's ability to make the drug. Second, an improved, next-generation Restasis would provide a competitive advantage and more years of patent protection for the improved product. Allergan is also now conducting a phase 2 clinical trial for a next-generation dry eye therapy called Restasis X. The company would not comment on a possible timetable for approval of the next-generation product.

Short-course steroids can help

Because Restasis takes a while to begin to work, Dr. Pflugfelder often starts his dry eye patients with a short course of topical steroids, which lasts about a month. "The topical steroid does two things," he says. "It provides earlier relief for the patient and it mitigates the burning or stinging sensation that many patients feel when they begin Restasis."

TREATMENT PLANS AND TIPS
Dr. Pflugfelder's treatment plan

The cornea specialists interviewed for this article agree that Restasis must be part of an overall treatment plan. It is not a panacea that can stand on its own. "No single drug can work for all patients," says Dr. Pflugfelder. "An overall treatment plan for dry eye disease could include one or more of the following: supplements such as fish oil, the antibiotic anti-inflammatory doxycycline, punctal plugs and the antibiotic AzaSite (azithromycin, InSite Vision, Alameda. Calif.)."

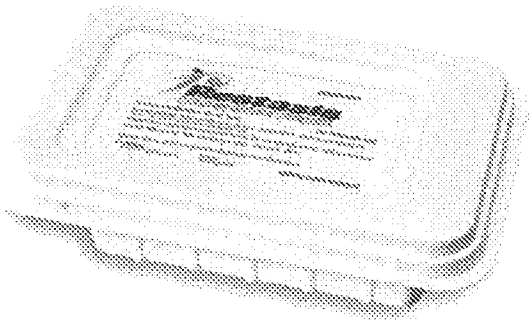
About 80% of the patients to whom he prescribes the drug do well on it, Dr. Pflugfelder says. "I have patients who have gone from debilitating dry eye to functioning very well. Another benefit is that these patients can decrease the use of artificial tears."

The doctor is also a patient

Christopher Starr, MD, FACS, of New York-Presbyterian Hospital, Weill Cornell Medical Center in New York, was just completing his fellowship training when Restasis was launched in the United States a decade ago. "I have had the benefit of being able to prescribe Restasis for my entire career," he notes. "I consider it the foundation of my dry eye treatment plan."

Dr. Starr also has dry eyes and uses the drug himself with good effect. "I keep it in my medicine cabinet, right near my toothbrush, because that way I'm sure to use it," he laughs.

Unlike Dr. Pflugfelder, who recommends patients refrigerate Restasis to reduce any stinging sensation from instilling the drug, Dr. Starr has never found the need to refrigerate it himself because he feels the drop is comfortable upon instillation.



Dr. Starr's treatment plan

"I liked Restasis from the beginning and I have increased my prescribing of it over the years as I've gained more experience and witnessed its impressive results," says Dr. Starr. The definition of dry eye disease has changed as knowledge of the disease continues to grow, he notes. "The most recent definition of dry eye disease from the Dry Eye WorkShop (DEWS) report notes hyperosmolarity and inflammation as key pathophysiologic factors, which supports the use of anti-inflammatory medication such as Restasis."

Dr. Starr agrees that treating dry eye disease requires an overall treatment plan tailored to each patient because dry eye is a multi-factorial disease. "I start most patients with early moderate and higher disease severity on Restasis because those patients are more likely to have significant ocular surface inflammation," he says. "A short course of the topical steroid Lotemax (lotoprednol, Bausch + Lomb, Tampa) with Restasis can be used to jump start the reduction of inflammation and help ease the mild burning associated with the initiation of Restasis."

Treating hyperosmolarity

Dr. Starr prescribes Restasis for most patients with significant hyperosmolarity as diagnosed by the TearLab device (TearLab Corporation, San Diego). Other elements of his dry eye treatment regimen can include AzaSite, which he finds helpful in treating anterior and posterior blepharitis off-label, omega-3 fatty acid supplementation, an emphasis on lid hygiene, warm compresses and lid massage, adjunctive use of artificial tears for symptom control and punctal plugs, among other treatments.

"We consider a decrease in the use of artificial tears a metric of success in treating this disease," Dr. Starr says. "A significant reduction in artificial tear use was seen in the pivotal clinical trials for Restasis."

Dr. Starr finds that educating patients in the proper use of Restasis is one of the primary keys to success with the drug. "First, patients must understand that Restasis is not an artificial tear and should not be used 'as needed,'" he says. "They should use one drop in the morning and one drop in the evening, no more and no less. They should expect some mild burning or stinging at first but a short-course of topical steroid and time will lessen this."

Dr. Starr says that some patients need as much as three to six months to obtain the full benefits of Restasis. This needs to be explained up front to maintain patient compliance through this initial period.

Dr. Yeu's treatment plan

Elizabeth Yeu, MD, of Virginia Eye Consultants in Norfolk, is another cornea specialist who both prescribes Restasis and uses it for her own dry eye condition. "I truly believe in the product for early-to-moderate dry eye," she says. "It does not work that well in the more severe case, stages three and four."

Dr. Yeu postpones using Restasis in patients who already have a burning sensation in their eyes. "First, we want to calm the eye down with a topical steroid before starting Restasis," she says. "If they have a foreign-body sensation or blurred vision but no burning we can start Restasis right away."

"Dr. Yeu says she postpones using Restasis in patients who already have a burning sensation in their eyes"

Episcleritis and lid inflammation

Dr. Yeu also likes to use Restasis for episcleritis, characterized by redness and inflammation. "With dry eye, you must customize the treatment for each patient," she says. "Younger patients tend to have more symptoms and few signs. For them, Restasis can be very helpful along with omega-3s. Older patients can be just the opposite, with strong signs and few symptoms. They don't seem to have the discomfort we see in younger patients. That could be because they have been on a number of medications and their senses have become a bit dulled over the years. But they do very well with Restasis, especially if they have a good tear film."

Dr. Yeu also treats inflamed lids as she wants to stop lid inflammation from spilling over onto and affecting the ocular surface. "I find that about 80% of my dry eye patients do very well on Restasis and just about all patients get some level of relief," she observes. "Patients who come off Restasis, for whatever reason, almost always get worse. Though they may not have seen improvement from the Restasis when they were using it, it was at least keeping the disease from getting worse. Restasis itself can only do so much, especially with patients who are dealing with other health factors that limit the effectiveness of the Restasis." **OM**

EXHIBIT M

Article Date: 11/1/2010

Dry Eye Drug Development: When Will the Floodgates Open?

New therapies have the potential to turn the prescription market from a trickle to a deluge.

By René Luthe, Senior Associate Editor

Clinicians waiting for a new prescription drug for their long-suffering dry eye patients are going to have to wait a little longer. While many drug makers are on the case, their offerings will not be an option in the near future. Allergan's Restasis remains the only game in town in the way of prescription remedies. "The regulatory approval process for dry eye drugs is a nightmare," concedes EyeGate Pharma's president and chief executive officer, Stephen From.

What gives? Miami's William B. Trattler, MD, allows that part of the problem may be the FDA setting the bar too high. Yet the main problem, he believes, is dry eye's own peculiar nature. "Dry eye can be caused by aqueous deficiency or it can be due to poor tear film quality related to Meibomian gland dysfunction," Dr. Trattler notes. "Or, it can be a combination of these two forms of dry eye. Importantly, inflammation is present in both conditions."

However, not all the news is discouraging: Some drugs are inching closer to approval and researchers continue to gain valuable insights into the disease. Here's a snapshot of prescription dry eye remedies on the horizon.

More Obstacles Than Most

The combination of factors at work in dry eye disease is widely held to be the main reason for the lack of progress on the new-drug front. "The disease itself is highly variable," says Simon Chandler, PhD, director of clinical research at Ista Pharmaceuticals.

Eddy Anglade, MD, chief medical officer at Lux Biosciences, agrees. "There isn't a very good correlation between signs and symptoms," he says, "so trying to find that group of patients who have disease that will respond in a way that is convincing from a regulatory standpoint is challenging, given that the current regulatory approval standard is to demonstrate significance in a sign and in a symptom."

It has been so difficult to achieve, Mr. From points out, that no company has succeeded in getting a New Drug Application (NDA) filing approved. Where many drugs run aground, he says, is in trying to transition from phase 2 clinical trials to phase 3. "Most people worry about translating from animal models into humans," Mr. From explains. "In dry eye, we worry about phase 2 data translating into phase 3 — can somebody repeat a study a second time?"

Other experts familiar with FDA clinical trials and dry eye disease concur. Dry eye's variability means that when it is time for sponsors to scale their phase 2 trials to phase 3, the drug's efficacy may be harder to demonstrate. The disease's multifactorial nature also contributes to the difficulty in navigating the approval process. For each different cause, there is at least one way to potentially treat it. Matching the drug to the right kind of patient is crucial (see "Clinical Trial Pearls," below).

Part of the problem might reside with the regulatory process itself. The process for clearance of a new drug is complex and as the knowledge base concerning dry eye disease expands, the scientific basis for drug testing changes. According to Michael A. Lemp, MD, clinical professor at Georgetown and George Washington universities, "it was anticipated that the FDA would issue new guidelines for clinical trials in dry eye disease several years ago, but these have not been made public. The delay may rest with senior management within the Agency."

The result is that there is no "one-stop shopping" source where would-be sponsors can learn the guidelines for clinical trial endpoints. Instead, sponsors must go to the FDA and make a proposal as to how they would perform a clinical trial; the FDA reviews the proposal and informs the sponsor if it is acceptable, or which portions are acceptable or unacceptable.

"While the FDA is quite open to these inquires and willing to listen to novel ap proaches, many times companies new to this field feel as if they are guessing what the FDA wants," Dr. Lemp explains. "They wonder if the FDA has changed what is acceptable since the last time they heard. It's like trying to read the tea leaves."

Chugging Along

Despite the regulatory hurdles, some dry eye drugs are making slow but steady progress toward beleaguered physicians and their patients. Most are anti-inflammatories, so their approval would fulfill a wish of Dr. Trattler's. "I use pulses of topical steroids frequently for dry eye patients, and if there were additional anti-inflammatory drugs that could work in this area, that would be very helpful for patients, since dry eye is an inflammatory condition."

• **EGP-437.** The closest drug to the goal is EyeGate's EGP-437. Currently in a phase 3 efficacy study, it's a dexamethasonederived corticosteroid solution delivered to the eye via an iontophoretic drug delivery system that enables the drug to overcome the problem of low bioavailability that limits other topical agents. "You have to try to bypass natural barriers that are in place: the tear film and cornea," Mr. From says. "It's very difficult to get a large quantity of drug into the front of the eye, or any drug to the posterior pole of the eye for retinal diseases." Iontophoresis also allows EGP-437 to bypass the method physicians have had to resort to deliver large quantities of drug into the eye: needles.

The doughnut-shaped applicator holds a sponge saturated with drug; the applicator is placed on the sclera after a topical anesthetic is applied to prevent the patient's blinking. An electrode at the base of the applicator is connected to a small, handheld generator that supplies a charge. A negatively charged drug in the foam portion gets a negative charge to the electrode, thus using the principle of electrorepulsion to push the drug at a high velocity into the eye.

The process, Mr. From says, requires only a couple of minutes. "Depending on how high the current is, or how long we leave this on the eye, will dictate how much drug goes into the eye and how deep it penetrates into the eye."

EGP-437 is a small molecule. In its recently-completed phase 2 study, it was able to treat multiple signs and symptoms of dry eye, rather than just one in each category, Mr. From says, "So we actually had the lucky advantage of being able to choose the best sign and the best symptom for our phase 3 trial." Even better, he says, was its onset of action, which begins within hours. "If you're a Sjögren's patient and you have severe dry eye, you are in a lot of discomfort and pain" and at risk for scarring, Mr. From explains. Such patients would welcome a therapy with rapid onset of action. "No other drug that I'm aware of works as quickly as our drug is working," he says.

Although data from EyeGate's 83-patient phase 2 trial are not yet available, the company did say that staining decreased in both fluorescein and lissamine green dyes, that conjunctival redness was reduced and that tear film breakup time increased.

As for dosage, the drug would be administered in a physician's office, probably on a quarterly basis, according to Mr. From, depending on severity. The company has begun

enrolling patients for the phase 3 clinical trial of approximately 180 planned. Mr. From anticipates that the trial should be completed during the first quarter of 2011, with top-line data available at the end of that period.

He describes EyeGate's approach as acute therapy for a chronic problem. "We are able to put so much drug in so quickly to the tissues of the eye that we're knocking down the inflammatory cascade very rapidly. The drug doesn't stay in the eye very long, but the pharmacological effect lasts for a long time."

• **CF101.** Can-Fite BioPharma Ltd. recently opened an Investigational New Drug application (IND) with the FDA for a phase 3 study of its lead drug, CF101, for treatment of moderate to severe dry eye disease. Dr. Pnina Fishman, Can-Fite's CEO, says that CF101 exerts an anti-inflammatory effect and also an immunomodulatory one. The study will be initiated in few months.

An earlier phase 2 study, in which CF101 was taken orally as a monotherapy for 12 weeks, showed a statistically significant benefit in the clearing of fluorescein staining in the nasal, temporal, pupillary and inferior cornea, the company reports. CF101 also was found to be safe and well tolerated in the Phase 2. Further, the study showed a decrease in intraocular pressure in patients with dry eye, findings that have prompted Can-Fite to initiate a phase 2 clinical study for the drug's treatment of glaucoma.

The randomized, double-masked phase 3 trial will compare two oral doses of CF101 to placebo. Approximately 240 patients will be enrolled at multiple centers, to be treated for 24 weeks. The clinical endpoints are improvement of corneal fluorescein staining, tear production and dry eye symptom score.

• **Low-dose bromfenac.** Ista Pharmaceuticals' phase 2 trial of low-dose bromfenac (Remura) demonstrated improvement in both a key sign (lissamine green staining) and in symptoms (as measured by the Ocular Surface Disease Index) of dry eye in 38 patients over a six-week period. Further, patients treated with low-dose bromfenac maintained the improvement in signs and symptoms for 10 days after discontinuing treatment. The company is currently in the process of initiating the efficacy portion of the phase 3 program, which will entail two studies with a total of approximately 1,000 patients followed over a six-week period, according to Dr. Chandler. The safety portion of the phase 3 trial is tentatively scheduled to begin later this year and will comprise a six-month and a 12-month trial, with a total of approximately 4,000 patients.

Dr. Chandler notes that low-dose bromfenac could address the impact of inflammation on the ocular surface, a central feature of dry eye. "Controlling inflammation could both quiet the symptoms — that is, irritation, dryness, gritty, sandy feeling, burning in some cases — and improve the signs, such as staining, of ocular surface disease," he explains. The approach yields a dual benefit, Dr. Chandler contends, because of bromfenac's efficacy in dealing with pain as well as its ability to interrupt the inflammatory cycle, thereby allowing the ocular surface to heal. "There are very few medications that truly address the inflammatory cascade that is central to the disease while improving patient comfort," he says.

Although the inflammatory etiology of dry eye remains theoretical, Dr. Chandler says it does explain the results seen in the phase 2 open-label trial. Dr. Chandler contends that low-dose bromfenac has an onset of action that is "much faster" than the approximately eight weeks required for topical cyclosporine. In studies completed to date, he says, the drug produced a response rate that hovers around 70%.

Regarding safety, Dr. Chandler points out that higher-dose bromfenac studied in more than 1,600 patients did not result in any serious corneal adverse events; ocular adverse events observed in these studies resolved with no sequelae. From the perspective of global clinical experience with bromfenac, in about 19 million ophthalmic uses of the currently marketed higher concentration, there have been 22 serious corneal adverse events reported overall. Not all were considered drug related, Dr. Chandler points out, and most were in subjects who had undergone cataract surgery. "Lowering the concentration of bromfenac as we have done could further reduce the likelihood of severe corneal adverse events," he says. As part

of its commitment to patient safety, Ista has incorporated frequent monitoring of the cornea into the protocols for the large safety trials being planned.

• **SAR 1118.** Sarcode Corp. says that the phase 2 results for SAR-118, a topical small-molecule lymphocyte function-associated antigen-1 antagonist, showed clear improvements in signs and symptoms of dry eye at 12 weeks. The trial was a randomized, multisite, doublemasked study involving 230 subjects. Various dose levels (0.1, 1.0 and 5.0%) were compared to placebo, with subjects receiving the drops BID for 12 weeks. The primary objective measure was inferior corneal staining; major secondary measures were OSDI symptom score and tear production by Schirmer test. The company will present full details of the phase 2 study in spring 2011. Sarcode is currently preparing for a phase 3 trial to begin in mid-2011.

• **Mapracorat.** Bausch + Lomb is addressing the issue of tear hyperosmolarity in dry eye disease, which research suggests is a mechanism involved in ocular surface inflammation, with its selective glucocorticoid receptor agonist (mapracorat), currently in phase 2 trials. In vitro studies suggest mapracorat inhibits hyperosmolar-induced cytokine release and mitogenactivated protein kinase pathways in human corneal epithelial cells. Development of the compound continues to progress as a novel product with a new mechanism of action for the treatment of dry eye, according to B+L.

A study in the September 2010 issue of *Molecular Vision* showed it to have comparable activity to dexamethasone in combating inflammation. The investigators evaluated mapracorat's anti-inflammatory effects in an in vitro osmotic stress model that induced hyperosmolar conditions in cultured human corneal cells. The model stimulated the release of pro-inflammatory cytokines interleukin-6, interleukin-8 and monocyte chemotactic protein-1, and also altered the phosphorylation state of p38 and c-Jun N-terminal kinase (JNK), and the transcriptional activity of NFkappaB and AP-1. The researchers found that the incubation of cells with mapracorat inhibited hyperosmolarinduced cytokine release with potency comparable to the dexamethasone control group. Additionally, increased phosphorylation of p38 and JNK caused by hyperosmolarity was inhibited by mapracorat, and the compound caused a significant decrease in the hyperosmolar-induced rise in NFkappaB and AP-1 transcriptional activity.

• **RX-10045.** One of a class of medicines called resolvins, RX-10045 is a small-molecule lipid mediator that Resolvyx Pharmaceuticals says activates the body's own mechanisms for shutting off inflammation. It is administered as a topical eye drop. Resolvyx completed a phase 2 trial last year for chronic dry eye. In the randomized, placebo-controlled, 232-patient trial, RX-10045 produced dose-dependent, statistically significant improvement on the primary endpoints for both the signs and symptoms of dry eye, and was generally shown to be safe and well tolerated, the company says.

The phase 2 study examined three doses of RX-10045 and used a controlled adverse environment (CAE) simulator to measure corneal staining in a stressful drying environment, as well as daily patient diaries using a standard visual analog scale to assess symptom improvement over the course of the 28-day study. The drug produced a significant dosedependent improvement from baseline in symptoms recorded in daily patient diaries. It also reduced staining of the central cornea by 75% ($P<0.00001$) versus placebo, the difference approaching statistical significance ($P=0.11$). Additionally, the drug showed a significant improvement in CAE-induced staining in the inferior cornea and in the composite of central and inferior cornea, which also approached statistical significance over placebo ($P=0.09$).

Resolvyx says the phase 3 trial should begin by the end of the year.

• **AzaSite.** Currently there is no prescription product indicated for blepharitis, a void Inspire Pharmaceuticals would like to fill with AzaSite (azithromycin). The drug is already approved as a treatment for bacterial conjunctivitis, but it did not meet statistically significant endpoints in two phase 2 trials for anterior blepharitis last spring. Though a four-week trial did demonstrate improvement in measured signs and symptoms compared to placebo, statistical significance was not achieved for the primary endpoint of mean lid margin hyperemia.

On the secondary endpoints, however, Inspire president and chief executive officer Adrian Adams reports seeing some statistical significance in the areas of signs and symptoms. In the two-week trial, there were no statistically significant improvements for AzaSite compared to vehicle; this included the primary endpoint of clearing of lid debris.

The company says it will use the data obtained from these studies to continue to develop trial parameters using AzaSite as a treatment for both anterior and posterior blepharitis, and expects to refine the trial design through the end of this year. The refinement will include study populations and "seeking improved mappability for assessing and measuring signs and symptoms," says Mr. Adams. "With that, we are looking to utilize the photographic reading centers to maximize the trial."

Inspire anticipates completing the additional phase 2 AzaSite clinical work in 2011. The initiation of the phase 3 trial should begin sometime later next year.

• **LX-214.** Lux Biosciences' dose-ascending phase 1 trial showed that LX-214, a novel topical formulation of voclosporin, was well tolerated by healthy volunteers. There was no difference in tolerability between the vehicle control and the concentrations of drug tested (0.2% and 0.02%). In five subjects diagnosed with dry eye syndrome, the cohort "showed some improvement in their signs (measured by Schirmer's tear test) and symptoms (measured by the OSDI); most notably, the changes observed occurred in the relatively brief timeframe of the study, two weeks compared to what has been reported previously with cyclosporine emulsion," according to Dr. Anglade.

Voclosporin affects the immune response at the surface of the eye, he explains. "We think by controlling the local inflam matory response, it will allow the tear-producing lacrimal gland and the surface of the eye to heal and improve tear production.

LX-214 belongs to a class of agents known as calcineurin phosphatase inhibitors, developed by the company into a nanomicellar formulation. "This renders LX214, a highly insoluble compound, a solution as opposed to an emulsion," Dr. Anglade explains. He believes the drug's solution formulation will help make it better tolerated than cyclosporine emulsion.

Another advantage, says Dr. Anglade, is voclosporin's higher concentration. "A limitation of other forms of topical cyclosporine is that sufficiently high concentrations may not be achieved locally. The ability to achieve high local concentrations may translate into improved efficacy. We'll be able to assess that concept hopefully in the phase 3 when we do a large dose-ranging study."

Dr. Anglade adds that the company is planning a phase 2 proof-of-concept study for the near future.

• **Restasis X.** Allergan reports that it is currently testing a new variation of cyclosporine, Restasis X, in phase 2 clinical trials. The company is not able to speculate on expected timing for FDA approval.

In related news, in a study published in the August issue of the *British Journal of Ophthalmology*, researchers evaluated the efficacy and safety of two concentrations (0.05% and 0.1%) of cyclosporine A in aqueous solution compared to vehicle in treating the signs and symptoms of moderate-tosevere dry eye patients.[1] At Day 21, the 1% group showed statistically significant improvement ($p<0.05$) in four symptoms and three ocular signs; the 0.05% showed statistically significant improvement in three symptoms and three signs; and the vehicle-only group in two symptoms and two signs. According to the researchers, at Day 42, the 0.1% group performed demonstrated improvement in four symptoms, while the 0.05% group demonstrated improvement in one symptom and one sign.

Hope for The Future

Dr. Lemp's vantage point as a participant in many FDA trials gives him reason to believe that the regulatory situation for dry eye drugs will soon improve. "As we learn more about the pathological processes at work in dry eye disease, new treatment strategies are emerging and data to support new endpoints are being published," he notes.

For one thing, in a meeting earlier this year, the FDA's Wiley Chambers, MD, expanded the criteria for primary endpoints that the agency will accept, including studies that document a correlation between signs and symptoms. Included in that slide was a list of inflammatory cytokines in the tears and tear osmolarity. "That's new," says Dr. Lemp. "That's potentially big."

Patient-reported outcomes are gaining favor with the FDA as well. The most common vehicle for reporting patient symptoms has been the 100-point scale OSDI. However, showing the required 29-point improvement in symptoms has been onerous. It has required sponsors to find patients who were highly symptomatic — "Who at least start out with 50 to 60 points on the scale," Dr. Lemp says. "And that rules out 90% of the population with dry eye."

New studies re-examining the relationships between subjective patient changes and levels of disease severity, novel ways to assess patient-reported improvement and a better understanding of the relationship between signs and symptoms in dry eye disease all have the potential to open the door to less onerous but scientifically rigorous study designs, Dr. Lemp notes. He believes that this augurs well for demonstration of clinical efficacy and the appearance of an expanded therapeutic portfolio of drugs for the more effective management of dry eye disease.

Perhaps the best reason to believe that the fortunes of prescription dry eye drugs will improve? "Let's put it this way, to my knowledge, there are probably more than 30 drugs in the pipeline," says Dr. Lemp. Many companies are investing in the dry eye market, and not just "the usual suspects" such as Alcon, Allergan and B+L.

The fact that Restasis could generate an approximate half a billion dollars in revenue last year despite its demonstrated effect in only about 15% of the patients studied (according to the package label), indicates significant unmet medical need and a healthy bottom line for those willing to invest.

With industry on board and the FDA willing to update its clinical trial criteria, the conditions for victories seem to be increasingly in place. **OM**

Reference

1. Baiza-Durán L, Medrano-Palafox J, Hernández-Quintela E, Lozano-Alcazar J, Alaníz-de la O JF. A comparative clinical trial of the efficacy of two different aqueous solutions of cyclosporine for the treatment of moderate-to-severe dry eye syndrome. *Br J Ophthalmol.* 2010 Aug 1. [Epub ahead of print]

Clinical Trial Pearls

Ora, Inc. has been helping drug makers navigate clinical trials for 15 years, says George Ousler, director of the company's dry eye department, so they have a lot of experience in knowing what makes for a successful program. Here are his recommendations:

- **Identify proper inclusion/exclusion criteria.** Because there are many different causes of dry eye, and different medications that could potentially treat it, it is critical that companies take the time to match the medication's mechanism of action to the appropriate patient population.
- **Focus on both signs and symptoms.** Related to proper inclusion criteria, it is necessary to only include patients who show both signs and symptoms of dry eye. "It sounds pretty straightforward, but there's actually a fair amount of lack of correlation between the two," Mr. Ousler says.
- **Design well-controlled studies and standardize.** Certain clinical models enable better control for the endpoints of dry eye. Toward this end, Ora has developed the Controlled Adverse Environment (CAE). By controlling environmental factors such as humidity, temperature, air flow and visual tasking, "you can establish a screening tool to identify the right patient, and an endpoint to demonstrate efficacy. If it's better controlled, there's not so much background noise like traditional environmental studies," Mr. Ousler explains.

- **Reduce clinical sites.** This helps to keep the trial well controlled and standardized.
- **Enlist the right crew.** "It's more than just running a trial; you have to work with a group of people who understand the disease as well as the entire clinical/regulatory pathway," Mr. Ousler says.

Ophthamology Management, Issue: November 2010

EXHIBIT N

Company	Failed Compound
Alacrity	ALTY-0501
Alcon	Rejena (sodium hyaluronate 0.18%)
Alcon	Cilomilast (AL-38583)
Alcon	AL43546
Alcon	Durezol
Alcon	ESBA105
Bausch + Lomb	Mapracorat (BOL-303242-X)
EyeGate	EGP-437
InSite	AzasitePlus
Inspire	Prolacria (diquafosal tetrasodium)
ISTA	Remura

Company	Failed Compound
ISTA	Ecabet
ISTA	Xibrom
Lux	voclosporin
MacuSight	sirolimus
Novartis	ANZ885
Novartis	AIN457
OPKO Health	Civamide
Pfizer	tofacitinib (CP-690,550)
RegeneRx	RGN259
Santen	rivoglitazone (DE-101)
Santen	DE-110
Sirion	Zyclorin (cyclosporine)

EXHIBIT O

From the Triangle Business Journal
:http://www.bizjournals.com/triangle/stories/2010/08/23/daily31.html

Aug 25, 2010, 12:52pm EDT

Inspire shelves dry-eye drug, shifts focus with Allergan

Jeff Drew

After a decade of development and disappointment, Inspire Pharmaceuticals finally has put a stop to its efforts to win U.S. Food and Drug Administration approval of a dry eye drug now called Prolacria.

The Durham company on Wednesday unveiled a modified collaboration agreement with longtime partner Allergan (NYSE: AGN) that opens the way for Inspire to close the door on Prolacria and move its focus to pink eye treatment AzaSite and the company's promising cystic fibrosis program.

Investors hailed the new agreement, pushing up Inspire shares by 3.88 percent, to $4.66, in mid-day trading Wednesday.

Inspire twice saw its dry eye drug fail to outperform a placebo in the last stage of human testing. The company tried changing the drug's name and adjusted the end point of the phase III clinical trial but ended up with the same results.

After studying the potential of moving forward with Prolacria, Inspire and Allergan were ready to move on. But the complicated nature of their drug development deal – which involves another dry eye treatment, Restasis – left Inspire facing a significant and immediate revenue hit.

Inspire (Nasdaq; ISPH) receives royalties from Allergan on sales of Restasis and received payments from the Irish company for hitting development milestones on Prolacria. The previous terms called for a 30 percent reduction in Inspire's Restasis royalty rate of 7.5 percent if the company dropped the Prolacria program and didn't begin contributing to the marketing and promotion of Restasis.

The new terms keep Inspire's Restasis royalty rate unchanged at 7.5 percent for 2010, before reducing it by 3 percentage points in 2011, a further 0.25 percentage point in 2013, and a final 0.50 percentage point in 2014. The rate will remain at 3.75 percent until 2020, when the contract runs out.

Restasis generated $11.2 million in royalty revenue for Inspire during the second quarter, which ended June 30. That was up from $8.9 million in the year-ago quarter.

For the quarter, Restasis accounted for more than 40 percent of Inspire's total revenue of $27.3 million and topped AzaSite, which produced revenue of $9.6 million.

"This agreement provides clarity on the revenue stream and respective responsibilities of the parties in our ophthalmic collaboration," said Adrian Adams, president and CEO of Inspire, which has 240 employees.

Reporter e-mail: jdrew@bizjournals.com

Electronic Acknowledgement Receipt

EFS ID:	17119314
Application Number:	13967179
International Application Number:	
Confirmation Number:	8654
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Alexis Swan
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON5B (AP)
Receipt Date:	14-OCT-2013
Filing Date:	14-AUG-2013
Time Stamp:	16:28:52
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		17618CON5B-Response-to-NFOA.pdf	1478039 4e3848feaf89a73ac9317fd9d25000d1b11602c5	yes	18

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant summary of interview with examiner	7	7
	Applicant Arguments/Remarks Made in an Amendment	8	18

Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	17618CON5B-Exhibit-1.pdf	670148 d43c6d440b6bac54805bd50936ee968900 1a8f9d	no	26
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	17618CON5B-Exhibit-2.pdf	452124 312fb156acf1ee5b36c77f3d5c9608e9d365 b4ac	no	19
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Affidavit-traversing rejectns or objectns rule 132	17618CON5B-Exhibit-3.pdf	269817 60467d2777513aa6b96972fa56ad6d929b9 e4f6c	no	10
Warnings:					
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Information:					
5	Affidavit-traversing rejectns or objectns rule 132	17618CON5B-Exhibit-4.pdf	7072016 e9b31287d9350c7259b0d288ff61512da92 6e736	no	115
Warnings:					
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Information:					
		Total Files Size (in bytes):	9942144		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/967,179	Filing Date 08/14/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	10/14/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 24	Minus	** 25	=	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/PEGGY YARBOROUGH/

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/967,179	Filing Date 08/14/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT

10/14/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 24	Minus	** 25	=	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/PEGGY YARBOROUGH/

Docket No. 17618CON5B (AP)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 13/967,179	Group Art Unit: 1658
Filed: August 14, 2013	Confirmation No. 8654
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Attached herewith please find an interview summary.

Summary of the Interview begins at page 2.

SUMMARY OF INTERVIEW

Attendees, Date and Type of Interview

A telephone interview was conducted on November 7, 2013 and was attended by Examiner Cordero Garcia and Laura L. Wine.

Identification of Claims Discussed

The Claims were discussed.

Identification of Prior Art Discussed

U.S. Patent Application Publication No. 2005/0014691 (U.S. Application Serial No. 10/621,053, "the '691 Publication") was discussed.

Principal Arguments and Other Matters

The Applicants presented arguments that the '691 Publication did not disclose all claimed limitations. The Applicants also argued that a rejection under 35 U.S.C. 103(a) would be improper because the '691 publication should be disqualified under 35 U.S.C. 103(c) because the present application (US 13/967,179) and the '691 publication, at the time the invention of the present application was made, were owned by or subject to an obligation of assignment to Allergan, Inc.

Results of Interview

It was agreed that the '691 publication would be removed as a reference for rejection under 103(a) and that the Claims were allowable.

Respectfully submitted,

Date: November 7, 2013

/Laura L. Wine/_____
Laura L. Wine
Registration No. 68,681

Please send all inquiries and correspondence to:

Patent Department
Allergan, Inc. (T2-7H)
2525 Dupont Drive
Irvine, CA 92612
Telephone: 714/246-6996
Facsimile: 714/246-4249

Electronic Acknowledgement Receipt

EFS ID:	17345314
Application Number:	13967179
International Application Number:	
Confirmation Number:	8654
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Alexis Swan
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON5B (AP)
Receipt Date:	07-NOV-2013
Filing Date:	14-AUG-2013
Time Stamp:	19:02:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	17618CON5B-Interview-Summary.pdf	98431 2808faf8294f2164860ff8c877457c8fd17183d6	no	3

Warnings:	
Information:	

Total Files Size (in bytes):	98431

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	13967179
Filing Date	14-Aug-2013
First Named Inventor	Andrew Acheampong
Attorney Docket Number	17618CON5B (AP)
Title of Invention	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Allergan, Inc.	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

13649287 filed on 10/11/2012

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request.

○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 68681 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors ○ A joint inventor; all of whom are signing this request ○ The assignee of record of the entire interest that has properly made itself of record pursuant to 37 CFR 3.71

Signature	/Laura L. Wine/
Name	Laura L. Wine

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	13967179
Filing Date:	14-Aug-2013
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Alexis Swan
Attorney Docket Number:	17618CON5B (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Statutory or Terminal Disclaimer	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**160**

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 13967179

Filing Date: 14-Aug-2013

Applicant/Patent under Reexamination: Acheampong et al.

Electronic Terminal Disclaimer filed on November 25, 2013

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	17494637
Application Number:	13967179
International Application Number:	
Confirmation Number:	8654
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Alexis Swan
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON5B (AP)
Receipt Date:	25-NOV-2013
Filing Date:	14-AUG-2013
Time Stamp:	15:13:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$160
RAM confirmation Number	1974
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Electronic Terminal Disclaimer-Filed	eTerminal-Disclaimer.pdf	34349 b39a995245f319cfac6f9545f4c24444fd748cf6	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30795 c2e3addf3180fa6acc7adfe92d6edd035f448143	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65144		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

51957 7590 12/06/2013

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER
CORDERO GARCIA, MARCELA M

ART UNIT	PAPER NUMBER
1658	

DATE MAILED: 12/06/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/06/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 12/06/2013
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/06/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1658	514-020500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

51957 7590 12/06/2013

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IRVINE, CA 92612-1599

EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1658	

DATE MAILED: 12/06/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notices of Allowance and Fee(s) Due mailed between October 1, 2013 and December 31, 2013

(Addendum to PTOL-85)

If the "Notice of Allowance and Fee(s) Due" has a mailing date on or after October 1, 2013 and before January 1, 2014, the following information is applicable to this application.

If the issue fee is being timely paid on or after January 1, 2014, the amount due is the issue fee and publication fee in effect January 1, 2014. On January 1, 2014, the issue fees set forth in 37 CFR 1.18 decrease significantly and the publication fee set forth in 37 CFR 1.18(d)(1) decreases to $0.

If an issue fee or publication fee has been previously paid in this application, applicant is not entitled to a refund of the difference between the amount paid and the amount in effect on January 1, 2014.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/967,179	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1658	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA L. WINE*. (4)_____.

Date of Interview: *17 October 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37,54 and 60*.

Identification of prior art discussed: *US 5,474,979 and US 6 984,623*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1658	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Authorization for communication under MPEP 502.03 was filed on 10/1/2013 by Applicant's representative.Courtesy copies of the OA and response were exchanged via email by Examiner (10/7/2013, see attachment of the email communication. Examiner emailed a courtesy copy of the OA on 10/7/2013). Applicant's representative emailed a courtesy copy of the response to the OA on 10/14/2013. The exchanged copies were identical to the OA and response of record, therefore, for the sake of clarity they have not been herein included) and Applicant's representative. Applicant's representative contacted Examiner on 10/17-18/2013,10/23/2013, 10/28/2013 and 10/30/2013 and 11/1/2013 to inquire about the application, provide updates regarding the status of the application and filings and/or discuss any potential questions and related applications. Examiner provided updates regarding the status of the examination as requested. On 10/18/2013, Examiner contacted Applicant's representative to discuss the affidavits EXHIBIT 1 and 2 were discussed specifically with regards to the excipients used in phase2 and phase3 of the clinical trials described therein, Applicant's representative indicated that the excipients were identical in these 2 phases and that this was also set forth in the affidavits, which was confirmed by Examiner (e.g., page 2, paragraph 8 of EXHIBIT 1). On 10/23/2013, Applicant's representative along with Maysa Attar contacted Examiner to discuss whether any outstanding questions remained from the examination of the courtesy copies of the affidavits. Examiner did not have any further questions and indicated that she would act on the case when the official papers were filed. Laura Wine contacted Examiner on 10/28/2013 indicating that the response had been filed on 10/23/2013. During the final search Examiner found a potential 103(a) reference (US 6 984,623, Table 5) on 11/4/2013. Applicant's representative filed a statement of common ownership for US 6984623 (corresponding to US 2005/0014691) and the instant application. The statement is deemed sufficient to obviate an obviousness rejection over US 6,984,623. Furthermore, in telephonic conversations on 11/8/2013, 11/15/2013 and 11/20/2013 Applicant's representative inquired about the status of the instant application. Examiner indicated that she would contact Applicant's representative whenever examination proceeded. In a telephonic conversation on 11/25/2013 Examiner further discussed and requested a TD for 13/649,287 in order to obviate potential ODP rejections. The TD was filed and approved on 11/25/2013.

Notice of Allowability	Application No. 13/967,179	Applicant(s) ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO GARCIA	Art Unit 1658	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10/07/2013, 10/14/2013 and 11/07/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *37-57, 59-61*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20131120* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. This Office Action is in response to the replies received on 10/07/2013, 10/14/2013 and 11/07/2013.

Any rejection from the previous office action, which is not restated here, is withdrawn.

Status of the claims

3. Claims 37-61 were pending in the application. Claims 37, 44, 47, 49, 50, 51, 52, 53, 54, 57, 60 have now been amended. Claim 58 has been cancelled. Claims 37-57, 58-61 are presented for examination on the merits.

Declarations under 37 CFR 1.132

4. The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 3 comprising EXHIBITS A, B and C) has been carefully considered, however it is deemed insufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: "Objective evidence of nonobviousness including commercial success must be commensurate in scope with the claims. *In re Tiffin*, 448 F.2d 791, 171 USPQ 294 (CCPA 1971) (evidence showing **commercial** success of thermoplastic foam "cups" used in vending machines was not commensurate in scope with claims directed to thermoplastic foam "containers" broadly). In order to be commensurate * > in < scope with the claims, the **commercial** success must be due to claimed features, and not due to unclaimed

features. *Joy Technologies Inc. v. Manbeck*, 751 F. Supp. 225, 229, 17 USPQ2d 1257, 1260 (D.D.C. 1990), *aff'd*, 959 F.2d 226, 228, 22 USPQ2d 1153, 1156 (Fed. Cir. 1992) (Features responsible for **commercial** success were recited only in allowed dependent claims, and therefore the evidence of **commercial** success was not commensurate in scope with the broad claims at issue." (MPEP 716.03). In the instant case, compositions comprising any of the previously discussed embodiments of Ding et al. (i.e., Examples D, E) were not commercially available nor were compared in the declaration. Therefore, Examiner cannot ascertain whether the commercial success of the claimed composition was due to the claimed features which are distinct from those embodiments in Ding et al. or other factors such as the fact that the composition was the only composition for treating dry eyes FDA approved and thus, commercially available for sale to the public (see, e.g. EXHIBIT 4, pages 4-5, paragraphs 8-9).

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 4, comprising EXHIBITS A-O) is insufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: "Establishing **long-felt need** requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of **long-felt need** and the failure of others to the issue of obviousness depends on several factors: (I) First, the need must have been a persistent one that was recognized by those of ordinary skill in the art; (II) Second, the **long-felt need** must not have been satisfied by another before the invention by applicant and (III) Third, the invention must in fact satisfy the long-felt need (MPEP 716.04). In the instant case, with

respect to (II), the prior art abundantly provides for methods of treating dry eye disease with cyclosporin and other active agents, e.g., Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013), Kawashima et al. (US 6,582,718, cited in the IDS dated 9/11/2013), Ding et al. (US 5,981,607, cited in the IDS dated 9/11/2013) and Benita et al. (US 6,656,460, cited in the IDS dated 9/12/2013). Therefore, (II) has not been met and the arguments regarding long-felt need have not been deemed persuasive.

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 1, comprising EXHIBITS A-F) is deemed sufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) 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% 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. The data represents a comparison of the subpopulation of Phase 2 patients using compositions with the same reductions in tear production (5 mm/5 min) as those enrolled in the Phase 3 studies. EXHIBIT 1 at paragraph 8. All of the cyclosporin A-containing formulations as well as the vehicle also included 2.2% by weight glycerine, 1.0% by weight polysorbate, 0.05% Pemulen, sodium hydroxide, and water (see paragraph 6, page 2 of EXHIBIT 1).

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). The excipients were the same in the compared compositions. Given that the compositions comprise the same amount of active agent (0.05 % cyclosporin A) as Ding 1E, the improvements are surprising, unexpected and commensurate in scope with the claimed invention.

The declaration under 37 CFR 1.132 filed 10/14/2013 (EXHIBIT 2, comprising EXHIBITS A-D) is deemed sufficient to overcome the rejection of claims 37-61 based upon Ding et al. (US 5,474,979, cited in the IDS dated 9/11/2013) as set forth in the last Office action because: EXHIBITS A-D were carefully reviewed. As described in paragraph 7 of the EXHIBIT 2, the chart in EXHIBIT B shows that the amount of cyclosporin A that reaches the cornea and conjunctiva, ocular tissues that are highly relevant for the treatment of dry eye or keratoconjunctivis sicca, is higher for the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) than the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil (the claimed formulation) relative to the formulation containing 0.1% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D). According to Dr. Attar, this data teaches that the formulation containing 0.05% by weight cyclosporin A and 1.25% by weight castor oil would be less therapeutically effective

than the formulation containing 0.05% by weight cyclosporin A and 0.625% by weight castor oil or the formulation containing 0.10% by weight cyclosporin A and 1.25% by weight castor oil. EXHIBIT A, paragraph 8. Therefore it would be unexpected that the composition with lower uptake in cornea and conjunctiva would have significantly improved activity.

Taking the results of the studies and data presented in the EXHIBITS 1 and 2 together, it is clear that the specific combination of 0.05% by weight cyclosporin A with 1.25% by weight castor oil is surprisingly critical for therapeutic effectiveness in the treatment of dry eye or keratoconjunctivitis sicca.

Accordingly, the Declarations in EXHIBIT 1 and EXHIBIT 2, together with the data presented in those declarations, provide clear and convincing objective evidence that establishes that the claimed formulations, including 0.05% by weight cyclosporin A and 1.25% by weight castor oil, demonstrate surprising and unexpected results, including improved Schirmer Tear Test scores and corneal staining scores (key objective measures of efficacy for dry eye or keratoconjunctivitis sicca) and improved visual blurring and reduced artificial tear use as compared to the prior art, for example, emulsion formulations disclosed in Ding et al., including formulations with 0.05% by weight cyclosporin A and 0.625% by weight castor oil (Ding et al. 1E) and formulations with 0.10% by weight cyclosporin A and 1.25% by weight castor oil (Ding et al. 1D) which are the closest prior art formulations. The unexpected results are commensurate in scope with the claims (MPEP 716.02(d)).

Thus, the obviousness rejection in view of Ding et al. is herein withdrawn.

Double Patenting

5. The ODP rejection over Ding et al. is herein withdrawn for the reasons set forth in section 4 above.

Statutory double patenting rejection

6. The statutory double patenting rejection over 13/961,818 is withdrawn in view of Applicants' amendments to the instant claims and those of the cited application.

Terminal disclaimers

7. Terminal disclaimers for 13/961,168; 13/967,163; 13/961,828; 13/967,189; 13/961,808; 13/961,818, 13/61,835 were received and accepted on 10/7/2013. Therefore, the ODP rejections of record and potential ODP for 13/961,818 -as now amended- have been withdrawn.

Further, upon reconsideration, Examiner also requested a TD for 13/649,287 in a further telephonic communication on 11/25/2013. This TD was received and accepted on 11/25/2013

Examiner contacted Applicant's representative on 11/7/2013 and discussed US 6,984,628. In order to obviate a potential obviousness rejection over US 6,984,628 (corresponding to US 2005/0014691, cited in the IDS dated 9/11/2013), Applicant's representative filed a statement on 11/7/2013 that the '691 Publication should be disqualified under 35 U.S.C. 103(c) because the present application and the '691 publication, at the time the invention of the present application was made, were owned by or subject to an obligation of assignment to Allergan, Inc. The statement was carefully considered and deemed persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1658

MMCG 11/2013

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/967,179	ACHEAMPONG ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1658	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MARCELA M. CORDERO GARCIA*. (3)_____.

(2) *LAURA L. WINE*. (4)_____.

Date of Interview: *17 October 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☒102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *37,54 and 60*.

Identification of prior art discussed: *US 5,474,979 and US 6 984,623*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/MARCELA M CORDERO GARCIA/ Primary Examiner, Art Unit 1658	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Authorization for communication under MPEP 502.03 was filed on 10/1/2013 by Applicant's representative.Courtesy copies of the OA and response were exchanged via email by Examiner (10/7/2013, see attachment of the email communication. Examiner emailed a courtesy copy of the OA on 10/7/2013). Applicant's representative emailed a courtesy copy of the response to the OA on 10/14/2013. The exchanged copies were identical to the OA and response of record, therefore, for the sake of clarity they have not been herein included) and Applicant's representative. Applicant's representative contacted Examiner on 10/17-18/2013,10/23/2013, 10/28/2013 and 10/30/2013 and 11/1/2013 to inquire about the application, provide updates regarding the status of the application and filings and/or discuss any potential questions and related applications. Examiner provided updates regarding the status of the examination as requested. On 10/18/2013, Examiner contacted Applicant's representative to discuss the affidavits EXHIBIT 1 and 2 were discussed specifically with regards to the excipients used in phase2 and phase3 of the clinical trials described therein, Applicant's representative indicated that the excipients were identical in these 2 phases and that this was also set forth in the affidavits, which was confirmed by Examiner (e.g., page 2, paragraph 8 of EXHIBIT 1). On 10/23/2013, Applicant's representative along with Maysa Attar contacted Examiner to discuss whether any outstanding questions remained from the examination of the courtesy copies of the affidavits. Examiner did not have any further questions and indicated that she would act on the case when the official papers were filed. Laura Wine contacted Examiner on 10/28/2013 indicating that the response had been filed on 10/23/2013. During the final search Examiner found a potential 103(a) reference (US 6 984,623, Table 5) on 11/4/2013. Applicant's representative filed a statement of common ownership for US 6984623 (corresponding to US 2005/0014691) and the instant application. The statement is deemed sufficient to obviate an obviousness rejection over US 6,984,623. Furthermore, in telephonic conversations on 11/8/2013, 11/15/2013 and 11/20/2013 Applicant's representative inquired about the status of the instant application. Examiner indicated that she would contact Applicant's representative whenever examination proceeded. In a telephonic conversation on 11/25/2013 Examiner further discussed and requested a TD for 13/649,287 in order to obviate potential ODP rejections. The TD was filed and approved on 11/25/2013.

Notice of References Cited	Application/Control No. 13/967,179	Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL.	
	Examiner MARCELA M. CORDERO	Art Unit 1658	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,984,628	01-2006	Bakhit et al.	514/20.8
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2	"6,984,628".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2013/11/23 13:46
L2	19	cyclosporin same "0.05" same castor same "1.25"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2013/11/23 14:18
L3	17	cyclosporin same "0.05" same castor same "1.25" and ("dry eye" or keratoconjunctivitis)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2013/11/23 14:18
L4	5	cyclosporin near3 "0.05" same castor near3 "1.25" and ("dry eye" or keratoconjunctivitis)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2013/11/23 14:20
L5	5	cyclosporin near3 "0.05" same castor near3 "1.25" and ("dry eye" or keratoconjunctivitis) and emulsion	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2013/11/23 14:22

EAST Search History (Interference)

<This search history is empty>

11/23/2013 2:29:12 PM

Cordero Garcia, Marcela M.

From: Wine_Laura <Wine_Laura@Allergan.com>
Sent: Thursday, November 07, 2013 12:21 PM
To: Cordero Garcia, Marcela M.
Subject: FW: Courtesy Copy of Response to Office Action Filed 10/14/13 - US 13/967,179 (17618CON5B)
Attachments: 17618CON5B Response to NFOA.DOCX; 17618CON5B-Exhibit-1.pdf; 17618CON5B-Exhibit-2.pdf; 17618CON5B-Exhibit-3.pdf; 17618CON5B-Exhibit-4 - 132 Declaration ONLY - Copy.pdf

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From: Wine_Laura [mailto:wine_laura@Allergan.com]
Sent: Monday, October 14, 2013 2:00 PM
To: marcela.corderogarcia@uspto.gov
Cc: Condino_Debra
Subject: Courtesy Copy of Response to Office Action Filed 10/14/13 - US 13/967,179 (17618CON5B)

Dear Examiner Cordero Garcia,

Attached for your review, please find a courtesy copy of our response to the 10/11/13 non-final office action for US 13/967,179 (AGN reference: 17618CON5B) and associated documents that we filed earlier today. Please feel free to give me a call if you have any questions or concerns.

Please note that Exhibit 4 ("Schiffman Declaration 2") is the 132 Declaration only. The file with all of the attachments to the declaration was too large to send you over email, but they were filed on EFS. Please let me know if you would like me to email you any of the Exhibits from this declaration.

Best Regards,

Laura

Laura Wine
Associate Patent Counsel
Allergan, Inc.
Wine_Laura@allergan.com

2525 Dupont Drive
T2-7
Irvine, CA 92612
Tel: 714-246-6996
Fax: 714-796-3043

Cordero Garcia, Marcela M.

From: Wine_Laura <Wine_Laura@Allergan.com>
Sent: Thursday, November 07, 2013 12:23 PM
To: Cordero Garcia, Marcela M.
Subject: FW: 17618CON5B
Attachments: IFW-Search Notes.docm; Non-Final Rejection.docm; PTO-326 Office Action Summary.docm; PTO-413B Examiner-Initiated Interview Summary.docm; bibdatasheet.pdf; Amended Claim for 17618CON5B (4).pdf; EASTSearchHistory.13967179.10_07_2013.14_09_56.pdf; edan_IDS_09_11_2013 _HLHA4IMFPXXIFW3.pdf; Interview Agenda (3).pdf; STN.pdf

From: Cordero Garcia, Marcela M. [mailto:Marcela.CorderoGarcia@USPTO.GOV]
Sent: Monday, October 07, 2013 2:07 PM
To: Wine_Laura
Subject: 17618CON5B

Marcela M. Cordero Garcia
Patent Examiner
Art Unit 1658
Phone: 571-272-2939
Fax: 571-273-2939

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13967179	ACHEAMPONG ET AL.
	Examiner	Art Unit
	MARCELA M CORDERO GARCIA	1658

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
none	none	10/7/2013	MMCG

SEARCH NOTES		
Search Notes	Date	Examiner
STN search (attached)	10/7/2013	MMCG
EAST search (attached)	10/7/2013	MMCG
also ran PALM Inventor searchh	10/7/2013	MMCG
EAST updated (attached)	11/23/2013	MMCG
also ran PALM Inventor search	11/23/2013	MMCG

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
EAST search	attached	11/25/201333	MMCG

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13967179	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1658

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	24	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1658	11/25/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13967179	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1658

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	20.5	A	6	1	K	38 / 13 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	24	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1658	11/25/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13967179	ACHEAMPONG ET AL.
	Examiner	**Art Unit**
	MARCELA M CORDERO GARCIA	1658

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	24	
/MARCELA M CORDERO GARCIA/ Primary Examiner.Art Unit 1658	11/25/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

51957 7590 12/06/2013
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Lauren Barberena	(Depositor's name)
/Lauren Barberena/	(Signature)
December 6, 2013	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)	8654

TITLE OF INVENTION: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$0	$0	$1780	03/06/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
CORDERO GARCIA, MARCELA M	1658	514-020500

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Laura L. Wine
2 Joel German
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Allergan, Inc.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Irvine, California

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 01-0885 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Laura L. Wine/ Date December 6, 2013

Typed or printed name Laura L. Wine Registration No. 68,681

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Acheampong, *et al.*	Examiner: Marcela M Cordero Garcia
Serial No.: 13/967,179	Group Art Unit: 1658
Filed: August 14, 2013	Confirmation No. 8654
For: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS	Customer No.: 51957

COMMENTS ON EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE AND INTERVIEW SUMMARY

Mail Stop - Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Statement of Reasons for Allowance in the Notice of Allowance mailed December 6, 2013, Applicant respectfully submits the following comments.

Summary of Interviews begin on page 2 of this paper.

Comments on Statement of Reasons for Allowance begin on page 3 of this paper.

SUMMARY OF TELEPHONE INTERVIEW

Attendees, Date and Type of Interviews

Telephone interviews were conducted on October 18, 2013, November 4, 2013, November 7, 2013, and November 25, 2013 and attended by Examiner Marcela M Cordero Garcia and Laura L. Wine. Laura L. Wine also contacted the Examiner on October 17, 2013, October 23, 2013, October 28, 2013, October 30, 2013, November 1, 2013, November 8, 2013, November 15, 2013 and November 20, 2013 to inquire regarding the status of the application. Dr. Mayssa Attar was also present for the October 23, 2013 status inquiry.

Identification of Claims Discussed

The Claims were discussed, focusing on Claims 37, 54, and 60.

Identification of References Discussed

On October 18, 2013, U.S. Patent No. 5,474,979 to Ding et al. was discussed. On November 4 and 7, 2013, U.S. Application Serial No. 10/621,053 (published as U.S. Patent Application Publication No. 2005/0014691 and issued as US 6,984,628 to "Bakhit") was discussed. On November 25, 2013, U.S. Patent Application Serial No. 13/649,287 was discussed.

Principal Arguments and Other Matters

On October 18, 2013 Laura L. Wine and Examiner Cordero Garcia discussed the response and exhibits filed in the October 14, 2013 response to non-final office action.

On November 4, 2013 the Bakhit reference was discussed. On November 7, the Bakhit reference was also discussed. The substance of the November 7 interview is addressed in the Applicant's interview summary filed on November 7, 2013.

On November 25, 2013 U.S. Patent Application Serial No. 13/649,287 was discussed. While the Applicants do not acquiesce to any potential provisional obviousness-type double patenting rejections over the claims of this reference, in order to expedite prosecution, a terminal disclaimer was filed over this copending application and accepted on November 25, 2013.

Results of Interviews

It was agreed that the Applicants would file a terminal disclaimer over U.S. Patent Application No. 13/649,287. The Examiner also agreed that the Claims were allowable.

COMMENTS ON STATEMENTS OF REASONS FOR ALLOWANCE

Applicants respectfully submit the following comments on the Examiner's Statement of Reasons for Allowance.

The Applicants respectfully disagree with the Examiner's determination that the evidence of Commercial Success presented in the October 14, 2013 response to Office Action, including the Declaration of Aziz Mottiwala filed under 37 CFR 1.132 and associated Exhibits, was insufficient to overcome the rejection of the Claims under 35 U.S.C. § 103(a) based on Ding et al. The Applicants also respectfully disagree with the Examiner's determination that the evidence of Long Felt Need presented in the October 14, 2013 response to Office Action, including the Declaration of Rhett M. Schiffman ("Schiffman Declaration 2") filed under 37 CFR 1.132 and associated Exhibits, was insufficient to overcome the rejection of the Claims under 35 U.S.C. § 103(a) based on Ding et al.

To the extent that there is any implication in such Statement that the patentability of the claims rests on the recitation of a single feature or the combination of particular features, Applicants respectfully disagree, since patentability rests on each claim taken as a whole. For example, Applicants submit that there are additional features from the claims that are not set forth in the cited art. Further, the Examiner's Statement refers to certain features of the claims. To the extent that the Examiner's Statement omits claim elements, groups claims together, or identifies purportedly distinguishing features of a claim or a group of claims, Applicants respectfully disagree with the Examiner's Statement. Rather, Applicants submit that the claims are allowable, because each claim, taken as a whole, recites a unique combination of features that is not anticipated or rendered obvious by the prior art.

Applicants also hereby traverse and respectfully reserve the right to traverse the characterizations of what any particular reference shows or teaches, or what any combination of references shows or teaches, or the appropriateness of combining references, and reserve the right to continue to do so in the future. In addition, Applicants respectfully traverse any characterizations of which references are deemed to be the closest prior art. Further, by making certain amendments to the claims, Applicants are not conceding that previously pending claims are not patentable. Rather, the amendments are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending

or other broader or narrower claims that capture any subject matter supported by the application's disclosure. Moreover, any arguments in support of patentability and based on a portion of a claim should not be taken as founding patentability solely on the portion in question; rather, it is the combination of features or acts recited in a claim taken as a whole which distinguishes it over the identified references.

Applicants attach herewith payment of the issue fee and requests that the application proceed to issuance. Should the Examiner have any concerns, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

December 6, 2013

/Laura L. Wine /

Laura L. Wine
Reg. No. 68,681

Laura Wine-T2-7H
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612
Direct: 714-246-6996
Fax: 714-246-4249

Electronic Patent Application Fee Transmittal

Application Number:	13967179
Filing Date:	14-Aug-2013
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Filer:	Laura Lee Wine/Lauren Barberena
Attorney Docket Number:	17618CON5B (AP)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	17590855
Application Number:	13967179
International Application Number:	
Confirmation Number:	8654
Title of Invention:	METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS
First Named Inventor/Applicant Name:	Andrew Acheampong
Customer Number:	51957
Filer:	Laura Lee Wine/Lauren Barberena
Filer Authorized By:	Laura Lee Wine
Attorney Docket Number:	17618CON5B (AP)
Receipt Date:	06-DEC-2013
Filing Date:	14-AUG-2013
Time Stamp:	15:35:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2080
RAM confirmation Number	2375
Deposit Account	010885
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	17618CON5B_ISSUE_FEE.pdf	107764 315a30b1929576f80a2f75dfbbca588c7a258d8e	no	2
Warnings:					
Information:					
2	Applicant summary of interview with examiner	17618CON5B_INTERVIEWSUMMARY.pdf	123761 fa0f4c4f383f0f47d7160bcbbbbd187152829b7d	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32457 24cb4915607d4c8d01aa6f84bfa7780e65d92aee	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	263982		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/967,179	08/14/2013	Andrew Acheampong	17618CON5B (AP)

CONFIRMATION NO. 8654

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

PUBLICATION NOTICE

OC00000065645072

Title:METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

Publication No.US-2013-0338083-A1
Publication Date:12/19/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Docket No. 17618CON5B (AP)

Change(s) applied to document, /T.M.S./ 12/10/2013

Amendments to the Specification

Please replace page 1, lines 6-10 of the specification filed herewith with the following amended paragraph:

This application is a continuation of copending U.S. Application Serial No. 13/961,818 filed August 7, 2013, which is a continuation of copending U.S. Application Serial No. 11/897,177, filed August 28, 2007, which is a continuation of U.S. Application Serial No. 10/927,857, filed August 27, 2004, now abandoned, which claimed the benefit of U.S. Provisional Application No. 60/503,137 filed September 15, 2003, which ~~is~~ are incorporated in ~~its~~ their entirety herein by reference.

Receipt date: 09/11/2013	Application Number	13967179 13967179 - GAU: 1658
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2013-08-14
	First Named Inventor	ACHEAMPONG, ANDREW
	Art Unit	1653
	Examiner Name	TBD
	Attorney Docket Number	17618-US-BCON5-AP

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

	75	6350442		2002-02-26	Michael Garst	
	76	6413547		2002-07-02	Bennett et al	
	77	6420355		2002-07-16	Richter et al	
	78	6468968		2002-10-22	Cavanak et al	
	79	6475519		2002-11-05	Meinzer et al	
	80	6486124		2002-11-26	Olbrich et al	
	81	6544953		2003-04-08	Tsuzuki et al	
	82	6555526		2003-04-29	Toshihiko Matsuo	
	83	6562873		2003-05-13	Olejnik et al	
	84	6569463		2003-05-27	Patel et al	
	85	6582718		2003-06-24	Yoichi Kawashima	

Change(s) applied to document, /R.M.L/ 12/13/2013

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/967,179	01/21/2014	8633162	17618CON5B (AP)	8654

51957 7590 12/31/2013

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Allergan, Inc., Irvine, CA, Assignee (with 37 CFR 1.172 Interest);
Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, NV;
James N. Chang, Newport Beach, CA;
David F. Power, Hubert, NC;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Eastern District of Texas, Marshall Division on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
2:14-cv-638	5/22/2014	Eastern District of Texas, Marshall Division

PLAINTIFF	DEFENDANT
ALLERGAN, INC.	ACTAVIS PLC, ACTAVIS, INC., WATSON LABORATORIES, INC., and ACTAVIS PHARMA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,633,162	1/21/2014	Allergan, Inc.
2	8,642,556	2/4/2014	Allergan, Inc.
3	8,648,048	2/11/2014	Allergan, Inc.
4	8,685,930	4/1/2014	Allergan, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**