U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA22388
Product Name:	(b) (4) (ACUVUE Theravision with Ketotifen)
Indication(s):	(b) (4) of ocular allergic itch due to allergic conjunctivitis
Applicant:	Johnson and Johnson Vision Care, Inc.
Dates:	Date Submitted: 04/30/2021
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Review Priority:	Standard
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Key words: ocular allergy, allergic conjunctivitis, contact lens, conjunctival allergen challenge (CAC) model.

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1 EXECUTIVE SUMMARY

This is a statistical review of the New Drug Application (NDA) submitted by Johnson and Johnson Vision Care, Inc (Applicant) for K-Lens, a combination product that incorporates the antihistamine ketotifen (see Drug Class Section) into etafilcon-A daily disposable contact lens. K-Lens is intended to provide vision correction for a specific range of refractive errors while simultaneously preventing ocular itching that is associated with allergic conjunctivitis. The proposed indication is: "as a daily disposable contact lens for correcting refractive ametropia (myopia and hyperopia) in phakic or aphakic patients who are suitable for contact lens wear and experience ocular allergic itch due to allergic conjunctivitis and who do not have red eye(s) or more than 1.00 D of astigmatism."

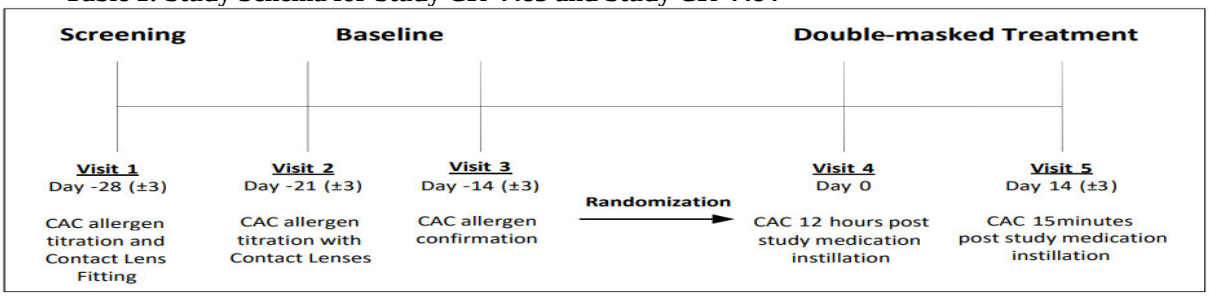
Per the Applicant, contact lens wearers who suffer from the discomfort associated with the signs and symptoms of ocular allergy experience an increased incidence of seasonal exacerbation of ocular allergy that commonly causes contact lens intolerance. Therefore, per the Applicant, K-Lens is developed to address an unmet need for the treatment of ocular allergy in contact lens-wearers.

This review will evaluate whether the safety and efficacy results in two pivotal Phase 3 studies, Study CR-4483 and Study CR-4484, submitted in this NDA, support the proposed indication. Both studies are multicenter, double-masked, randomized, parallel-group, placebo-controlled studies. The primary objective of these studies was to evaluate the safety and efficacy of K-Lens for the prevention of ocular itching associated with allergic conjunctivitis. The studies were conducted using the conjunctival allergen challenge (CAC) model[1]. Under this model, each study consisted of 5 visits over an approximate 6-week period. The initial 3 visits were designed to determine the allergen exposure necessary to achieve a positive ocular allergic reaction. At Visits 4 (Day 0), subjects were randomly assigned to 1 of the 3 treatment groups: [1] placebo lens administered bilaterally (placebo lens /placebo lens), [2] K-Lens administered bilaterally (K-Lens/K-Lens), or [3] K-Lens administered contralaterally (K-Lens/placebo lens). Note, placebo in these studies refers to etafilcon-A daily disposable contact lens without the drug component. Subjects were then rechallenged with the appropriate allergen dose 12 hours after lens insertion. At Visit 5 (Day 14), subjects received the same randomized lenses as assigned at Visit 4 and were challenged with the allergen 15 minutes after lenses insertion (Figure 1).

[1]*Reviewer's remark: Note, the CAC model is used as an alternative to traditional environmental allergy trials to evaluate antiallergy medications in a controlled environment. By varying the time between treatment and exposure to allergens, the CAC model is used in these studies to evaluate the onset and duration of action of K-Lens in preventing itching. At Visit 4 (Day 0), subjects are exposed to the CAC 12-hours after treatment installation. Consequently, the treatment comparison at this visit is intended to evaluate "the duration of action" of the drug (will the drug prevent itching 12 hours post-installation?). On the other hand, at Visit 5 (Day 14), subjects are exposed to the CAC 15-minutes after installation of treatment. Thus, the treatment comparison at this visit is intended to evaluate the "onset-of-action" of the drug (How quickly would the drug start working?).*

A total of 120 subjects in Study CR-4483 [(placebo/placebo; n=40), (K-Lens/K-Lens, n=39), (K-Lens/placebo, n=41)] and 124 subjects in Study CR-4484 [(placebo/placebo; n=42), (K-Lens/K-Lens, n=41), or (K-Lens/placebo, n=41)] were randomized to the three treatment arms in an approximately 1:1:1 ratio.

Table 1: Study Schema for Study CR-4483 and Study CR-4484



CAC=conjunctival allergen challenge

The primary efficacy endpoint was the mean ocular itching score evaluated at 3, 5, and, 7 minutes post CAC at Visits 4 (Day 0) and Visit 5 (Day 14). Note, ocular itching was evaluated by the subject using a 0 to 4 scale with half-unit steps [0=none and 4=incapacitating itch with irresistible urge to rub]. This endpoint is consistent with endpoints considered for this indication in previous submissions.

The primary efficacy analysis was conducted based on all randomized subjects (the ITT population) using a 2-sample t-test. The last observed ocular itching score (LOCF) from a prior timepoint within a given visit was used to impute missing ocular itching score. Note, although randomization was done at the subject level, for treatment comparisons, the unit of analysis was the eye. For example, in Study CR-4483, of the total of 240 eyes (from 120 subjects), 119 eyes were treated with K-Lens and the remaining 121 eyes were treated with placebo. Consequently, for the treatment comparison, the mean itching score from the 119 eyes treated with K-Lens was compared to the mean itching score from 121 eyes who received a placebo lens at each of the 6 time points (3, 5, 7 minutes at Visits 4 and 5). The Applicant's findings in both studies established that compared with placebo-treated eyes, K-Lens-treated eyes achieved a statistically significant reduction in mean ocular itching score at both the onset and duration of action study visits (Table 2 and Table 3).

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Reviewer's remarks: Note, the Applicant's primary efficacy analysis does not account for possible correlation in outcomes from two eyes from the same subject. Besides, because the analysis was conducted for each timepoint separately, the possible correlation among measurements taken from the same eye over time was not also considered. This reviewer conducted the analysis of the primary efficacy endpoint by accounting for possible correlations between outcomes from two eyes of the same subject and correlations among measurements from a given eye over time. The results of these analyses provided efficacy conclusions that are consistent with the Applicant's primary efficacy analysis and support the Applicant's efficacy claim.

Regarding safety, ocular adverse events (AEs) occurred in 9% of subjects (8% of eyes) in the K-Lens group compared to 3% of subjects (2% of eyes) in the placebo group. The Applicant reports that none of the ocular AEs were serious. The most common ocular AEs in the K-Lens group were eye pain, instillation site pain (each in 10 eyes [1.5%]) and eye irritation (11 eyes [1.7%]). Ocular AEs led to treatment discontinuation in 3 subjects (4 eyes) in the K-Lens group (conjunctivitis, corneal abrasion, dry eye, eye irritation, eye pruritus) and in 2 subjects (4 eyes) in the placebo group (conjunctivitis, viral conjunctivitis). Non-ocular AEs occurred in 22% of subjects in the K-Lens/K-Lens group and in 19% of subjects in the placebo/placebo group. The most common non-ocular AEs were nasopharyngitis (10 subjects [3.0%] in the K-Lens /K-Lens group and 2 subjects [1.2%] in the placebo/placebo group) and sinusitis (9 subjects [2.7%] in the K-Lens /K-Lens group and 1 subject [0.6%] in the placebo/placebo group).

Table 2: Primary Efficacy Endpoint Summary (Study CR-4483: ITT)

	K-lens	Placebo		
Visit (Time)	Mean (StdDev)	Mean (StdDev)		Diff(95% CI)
Day 0 (3 Min)	0.61(0.7)	1.71(0.89)		-1.1 (-1.31,-0.9)
Day 0 (5 Min)	0.74(0.73)	1.96(0.9)		-1.22 (-1.43,-1.01)
Day 0 (7 Min)	0.79(0.79)	1.86(0.94)		-1.07 (-1.29,-0.85)
Day 14 (3 Min)	0.42(0.66)	1.6(0.87)		-1.18 (-1.39,-0.98)
Day 14 (5 Min)	0.56(0.71)	1.82(0.91)		-1.26 (-1.47,-1.04)
Day 14 (7 Min)	0.54(0.7)	1.69(0.95)		-1.15 (-1.37,-0.93)

Table 3: Primary Efficacy Endpoint Summary (Study CR-4484: ITT)

	K-lens	Placebo		
Visit (Time)	Mean (StdDev)	Mean (StdDev)		Diff(95% CI)
Day 0 (3 Min)	0.75(0.83)	1.8(0.89)		-1.05 (-1.27,-0.83)
Day 0 (5 Min)	0.88(0.91)	2.04(0.88)		-1.16 (-1.38,-0.93)
Day 0 (7 Min)	0.86(0.91)	1.99(0.89)		-1.13 (-1.35,-0.9)
Day 14 (3 Min)	0.42(0.61)	1.72(0.94)		-1.3 (-1.5,-1.09)
Day 14 (5 Min)	0.56(0.72)	1.94(0.91)		-1.38 (-1.59,-1.17)
Day 14 (7 Min)	0.59(0.8)	1.83(0.98)		-1.24 (-1.47,-1.01)

Source: Adapted from Table 10 of the Applicant's Study Reports. ITT: Intent-to-treat.

Overall, the results of the Applicant's and the reviewer's analyses of ocular itching presented in this review provide evidence to support the efficacy of K-Lens for the treatment of ocular itching due to allergic conjunctivitis in contact lens wearers.

2 INTRODUCTION

This is a statistical review of the New Drug Application (NDA) submitted by Johnson and Johnson Vision Care, Inc referred to as the Applicant, on June 26, 2021, for K-Lens. K-Lens is a combination product that incorporates the antihistamine ketotifen into a daily disposable etafilcon-A contact lens. The proposed indication is as a daily disposable contact lens for correcting refractive ametropia (myopia and hyperopia) in phakic or aphakic patients who are suitable for contact lens wear and experience ocular allergic itch due to allergic conjunctivitis and who do not have red eye(s) or more than 1.00 D of astigmatism.

The primary evidence of efficacy and safety for this NDA comes from two identically designed Phase 3 studies (Study CR-4483 and Study CR-4484). Study CR-4483 enrolled 120 subjects in 2 sites while Study CR-4484 enrolled 124 subjects from 6 sites. All study sites are located within the united states.

The Applicant proposes to include findings from Study CR-4483 and Study CR-4484 into the "Clinical Studies" (Section 14) of the US Prescribing Information (USPI) to describe the efficacy of K-Lens in the treatment of ocular allergic itch due to allergic conjunctivitis. This review investigates whether the findings from these studies support the proposed indication and provides recommendations for the USPI to be considered by the Division of Ophthalmology (DO) if the product is approved.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the Applicant's summary of the specific studies reviewed.

2.1.1 Drug Class and Indication

The Applicant is developing K-Lens for the treatment of ocular itching associated with allergic conjunctivitis in contact lens wearers. Per the Applicant, K-Lens is a combination product that incorporates the antihistamine ketotifen into a daily disposable etafilcon-A contact lens. Ketotifen is the active ingredient in the currently marketed eye drop, ZADITOR® (ketotifen fumarate ophthalmic solution, 0.025%. ZADITOR® was originally approved as a prescription drug for the prevention of itching of the eye due to allergic conjunctivitis [NDA 0210166 (1999)] and switched to over the counter in 2006. Per the Applicant, the device component of this combination product is the etafilcon A daily disposable contact lens, marketed as 1•DAY ACUVUE® Brand Contact Lens (etafilcon A) for single use daily disposable wear based on pre-market approval (PMA) N18-033.

2.1.2 History of Drug Development

The original submission for this drug development was submitted under IND 66883, with the first pre-IND meeting held on November 24, 2003. During this pre-IND meeting, the Applicant

requested clarifications on the requirements for toxicology and CMC to support their planned IND and the draft clinical plan. Regarding the draft clinical plan, the Division of Ophthalmology (Division) noted that in the planned Phase 2 study, (b) (4) . The Division stated that this could lead to biased results given differences between the two eyes may tend to be magnified. The Division also stated that for an itching score graded based on a 9-point scale, the drug should show superiority over vehicle by at least a 2-step change at the majority of timepoints measured for the CAC trials. The Division also noted that the use of (b) (4) in the study will likely limit the ability of the results to be generalized to the overall contact lens population.

On December 1, 2006, the Applicant had an end-of-phase 2 meeting with the Division. During this meeting, the Applicant asked the Division if the Phase 3 study design, specifically, the dose to be evaluated, the 12 -hour lens wear time at the Visit 4 (duration of action), the primary endpoints, sample size and statistical analysis plan are acceptable. The Division stated that the sample size and the primary endpoints are acceptable. However, due to limited information provided in the submission, the Division was not able to comment on the acceptability of the dose to be evaluated and the outline of the planned trial. The Division recommended that the primary hypothesis be analyzed using a t-test with the Wilcoxon rank sum test included as a supportive analysis. The Division also advised the Applicant to address missing data issues.

On October 3, 2008, the Applicant had a pre-NDA CMC meeting with the Division to discuss plans for CMC sections of an NDA for K-Lens. On June 25, 2008, the Applicant had a second pre-NDA meeting with the Division to discuss the contents of the planned NDA submission for K-Lens. As part of the meeting discussion, the Applicant asked the Division if the Phase 3 efficacy trials are sufficient to support filing of the NDA. The Division responded by stating that the adequacy of the trials to support the proposed indication is a review issue. The Division however noted that, as topical application of the medication can be used for the same purpose in non-contact lens wearers, and there are additional risks involved in contact lens wear, this product should not be indicated for patients who do not already use contact lenses. The Division also stated that the indication should state that the product is indicated for the "prevention of itching of the eye associated with allergic conjunctivitis in daily wear contact lens users."

On April 2011, the Applicant had a Type-C meeting with the Division. As part of the meeting discussions, the Applicant asked the Division if the 12-hour duration of action endpoint in the Phase 3 pivotal efficacy studies support both the proposed indication and the proposed dosage and administration for this drug-device combination product. The Division disagreed. The Division stated that the pivotal studies would support the filing of an NDA, but the approval and labeling of the product is a review issue requiring complete review of an NDA. The Division reiterated its concern that the proposed product contraindicates the current warnings for contact lens use (i.e., to remove contact lenses if eyes are red). Per the Division, any proposed indication would need to address this concern, including, but not necessarily limited to changing the indication to: (b) (4) *is a daily disposable contact lens containing an H1 histamine receptor antagonist indicating for correcting refractive ametropia (myopia and hyperopia) and preventing itching associated with allergic conjunctivitis for up to 12 hours after lens insertion in contact lens wearers who do not have red eye or more than 1.00D of astigmatism.* The Applicant agreed with the Division's response and agreed to the proposed language with

regards to the red eye warnings for contact lens use in the indication section of the drug labeling. The Division also noted that the 12-hour duration of action would not be expected to cover a full waking day when the contact lens might be expected to be worn. The Division further stated that, consideration should be given to additional instructions for patients who continue to have itching after twelve hours.

On May 9, 2014, the Applicant had a Type-C meeting with the Division. The purpose of the meeting was to discuss the characterization of the K-Lens from the new manufacturer and the proposed bridging clinical study to support an NDA submission. As part of the clinical questions, the Applicant asked the Division if the average itching score from two eyes of the same subject could be considered as the unit of analysis for the planned bridging study, the Division agreed. Note, in all 3 prior efficacy studies (one Phase 2 and the two-Phase 3 CAC studies), the "eye" was the unit of analysis for the primary efficacy variables.

On August 3, 2015, the Applicant had a Type-C Pre-NDA meeting with the Division. The purpose of this meeting was to discuss the Applicant's plans for characterization of the K-Lens from the new manufacturer (a second change in a manufacturer) and to determine whether the proposed clinical studies are sufficient to support NDA submission for K-Lens.

On June 13, 2017, the Applicant had another meeting with the Division. In this meeting, the Applicant informed the Division that they plan to supplement the planned primary efficacy analysis with a sensitivity analysis that takes into account any potential correlation between left eye score and right eye score from the same subject using a linear mixed model for repeated measures. They asked the Division if this approach is acceptable. The Division stated that the proposed approach is acceptable and informed the Applicant to provide the mathematical form of the mixed model together with a sample SAS code. The Division also informed the Applicant to provide an explanation in the event this analysis result differs significantly from the primary analysis result which assumed outcomes from the left and right eyes are independent.

On February 17, 2021, the Applicant had a teleconference with the Division to discuss the proposed labeling configuration for K-Lens. The meeting focused on the Applicant's plan to differentiate K-Lens from other unmedicated ACUVUE® products and on the contents and formats of the drug labeling.

On March 23, 2021, the Applicant submitted a written response only pre-NDA meeting. The purpose of the meeting was to obtain concurrence from the Division on the appropriate content and format of an NDA submission. The Division agreed with the proposed content and format of an NDA submission for K-Lens and informed the Applicant to submit all SAS codes used to produce the study results.

2.1.3 Studies Reviewed

The Applicant's overall efficacy summary of studies CR-4483 and CR-4484 is presented in Table 4.

Table 4: Applicant's Efficacy Summaries

Design	Treatment	Endpoint/Analysis	Applicant's findings[2]
CR-4483 [1]MC, RD, DB, PG, PC	▪ K-Lens/K-Lens (n=39) ▪ K-Lens/ placebo (n=41) ▪ placebo/placebo (n=40)	**Primary Endpoint**: Mean ocular itching evaluated at 3, 5, and, 7 minutes post-allergen challenge conducted 12 hours post-study medication instillation (Visit 4; Day 0) and conducted 15 minutes post-study medication instillation (Visit 5; Day 14). The primary efficacy endpoint was analyzed by using a 2-sample t-test for both Visit 4 and Visit 5. The unit of analysis was the eye. Missing data was imputed using the last observation carried forward (LOCF) approach.	In the primary analysis in the ITT population, the efficacy of the K-Lens in relieving ocular itching was not only statistically significant ($p< 0.001$) at Visits 4 and 5, but also clinically significant with differences from placebo of more than 1 unit at 3, 5, and, 7 minutes post CAC.
CR-4484 [1]MC, RD, DB, PG, PC	▪ K-Lens/K-Lens (n=41) ▪ K-Lens/ placebo (n=41) ▪ placebo/placebo (n=42)	**Primary Endpoint**: Mean ocular itching evaluated at 3, 5, and, 7 minutes post-allergen challenge conducted 12 hours post-study medication instillation (Visit 4; Day 0) and conducted 15 minutes post-study medication instillation (Visit 5; Day 14). The primary efficacy endpoint was analyzed by using a 2-sample t-test for both Visit 4 and Visit 5. The unit of analysis was the eye. Missing data was imputed using the last observation carried forward (LOCF) approach within each visit.	In the primary analysis in the ITT population, the efficacy of the K-Lens in relieving ocular itching was not only statistically significant ($p< 0.001$) at Visits 4 and 5, but also clinically significant with differences from placebo of more than 1 unit at 3, 5, and, 7 minutes post CAC.

Source: Applicant's Study Report. [1]MC: multicenter, RD: randomized, DB: double-masked, PG: parallel-group, PC: placebo-controlled. [2] Randomization was done at the subject level. However, for treatment comparisons, the unit of analysis was the eye.

2.2 Data Sources

This NDA application was submitted electronically and includes full study reports as well as standardized datasets using SDTM and ADAM formats that are relevant for the analyses of studies CR-4483 and CR-4484 presented in this review. Datasets and corresponding definition files can be found at the following location: \\CDSESUB1\evsprod\NDA022388\0001. For each study, the following datasets submitted by the Applicant are used in this statistical review:

- adsl.xpt contains the demographic and disposition data
- D_Eye.xpt contains efficacy data including ocular itching
- adae.xpt contains the adverse event data
- DM.xpt contains demographic data

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the datasets and analyses conducted by the Applicant are acceptable. The data definition files, and reviewer's guide submitted in the NDA were sufficiently detailed to facilitate replication of the findings from the Applicant's primary analysis and other major analyses using the submitted datasets.

3.2 Evaluation of Efficacy

This section summarizes the design of studies CR-4483 and CR-4484 and the corresponding efficacy results submitted by the Applicant and produced by the reviewer's analyses.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

Studies CR-4483 and CR-4484 were multicenter, double-masked, randomized, parallel-group, placebo-controlled studies. These studies were designed to evaluate the safety and efficacy of K-Lens in contact lens wearers. To be eligible for these studies, subjects had to meet the following inclusion criteria:

- Adequately fitted with 1•DAY ACUVUE® by an optometrist or ophthalmologist at Visit 1.
- Had a Snellen Visual Acuity score of 20/30 or better in each eye at Visit 1 with spherocylindrical refraction.

- Had a Snellen Visual Acuity score of 20/30 or better in each eye with 1•DAY ACUVUE® at Visit 1.

- Had a correction from +6.00 to -12.00 diopters in each eye and astigmatism of -1.00 diopter or less in each eye.

- Had a positive history of ocular allergies and a positive skin test reaction to cat hair, cat dander, grasses, ragweed, and/or trees within the past 24 months.

- Manifested a positive bilateral CAC reaction (defined as ≥2.0 ocular itching and ≥2.0 hyperemia in 2 of the 3 vessel beds bilaterally) at Visits 1, 2, and 3.

- Able and willing to avoid all disallowed medications for the appropriate washout period (prior to Visit 1) and during the study trial period.

- Were current, successful soft contact lens wearers who had frequently worn contact lenses for at least 1 month or more prior to enrollment into the study.

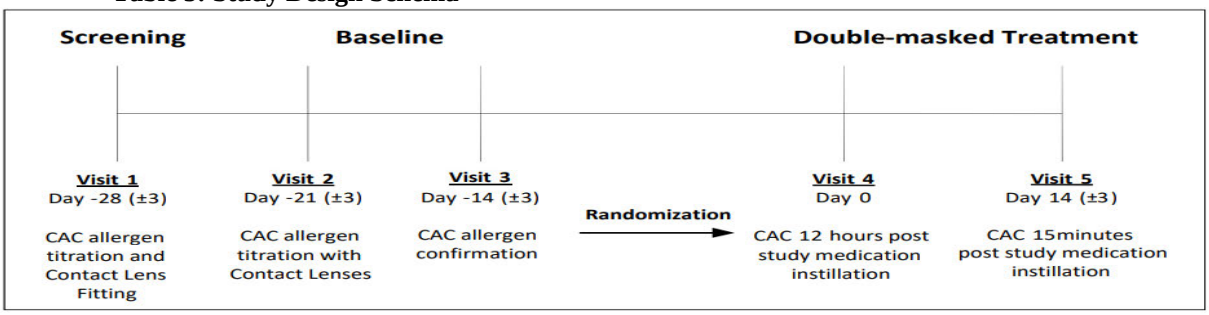
3.2.1.2 Randomization and Treatment

Both studies used a 1:1:1 randomization ratio for allocating eligible subjects to the three study treatments:

- Placebo lens administered bilaterally (placebo/placebo)
- K-Lens administered bilaterally (K-Lens/K-Lens)
- K-Lens administered contralaterally (K-Lens/placebo)

The total duration of both studies was 6 Weeks. The studies had 5 scheduled visits occurring at Day -28, Day -21, Day -1, Day 0, and Day 14. The initial 3 visits were designed to determine the allergen exposure necessary to achieve a positive ocular allergic reaction. At Visit 4, subjects were randomly assigned to 1 of 3 treatment groups: [1] placebo lens administered bilaterally (placebo/placebo), [2] K-Lens administered bilaterally (K-Lens/K-Lens), or [3] K-Lens administered contralaterally (K-Lens/placebo; Table 5).

Table 5: Study Design Schema



CAC=conjunctival allergen challenge

3.2.1.3 Escape Medications

The study protocols allowed for approved over the counter (OTC) anti-allergy eye drops to be administered by study staff in the office to subjects after all CAC evaluations are completed at each visit to relieve any ocular itching or redness.

3.2.1.4 Efficacy Endpoints

The primary efficacy endpoint of these studies was the mean ocular itching score evaluated at 3, 5, and, 7 minutes post CAC at Visits 4 (Day 0) and Visit 5 (Day 14). Ocular itching is evaluated by the subject using a 0 to 4 scale with half-unit steps [0=none and 4=incapacitating itch with irresistible urge to rub]. This endpoint is consistent with endpoints considered for this indication in previous submissions. The two studies evaluated the following secondary efficacy endpoints at 7, 15, and, 20 minutes post CAC at Visits 4 and 5:

1. Ciliary hyperemia
2. Conjunctival hyperemia
3. Episcleral hyperemia
4. Chemosis
5. Lid swelling
6. Mucous discharge
7. Tearing

Outcomes #1-#4 were evaluated by the investigator using a 0.5 increment scale where 0 = none and 4.0 = extremely severe. Outcome 5 was evaluated by the subject using a 4-point scale where 0 = none and 3 = severe). Outcomes 6 and 7 were evaluated by the subject as Absent and Present.

3.2.2 Statistical Methods

This section describes the statistical hypotheses, sample size calculation, analyses populations and the efficacy analyses presented in this review that are performed by the Applicant, as described in the statistical analysis plans (SAPs) for studies CR-4483 and CR-4483, as well as independent analyses performed by the statistical reviewer. All statistical analyses are performed at the 0.05 significance level (two-sided).

3.2.2.1 Statistical Hypotheses and Sample size

Hypothesis

The primary null and alternative hypotheses can be mathematically stated as follows:

$$H_o: \mu_{Ki} - \mu_{Pi} \leq 0$$
$$H_a: \mu_{Ki} - \mu_{Pi} > 0,$$

where μ_{Ki} and μ_{Pi} are the mean itching scores at time i for the K-Lens treated and placebo treated eyes, respectively.

A conclusion that K-Lens is superior to placebo lens at a given visit (Visit 4 or 5) is made if the mean ocular itching score for the K-Lens treated eyes is lower than placebo lens by at least 0.5 units for all time points tested at that visit and at least 1 unit for the majority of time points.

Sample size

In both studies, the Applicant calculates that a sample size of 120 eyes in each group (approximately 120 subjects) will have more than 90% power to detect a difference in means of 1.000. This sample size calculation assumes a mean itching score of 2.0 in the placebo group and a mean of 1.0 in the K-Lens, and a common standard deviation of 1.20 and a 0.050 two-sided significance level based on a 2-sample t-test.

3.2.2.2 Analysis Populations

The SAP of the studies defined the following analysis populations:

- The intent-to-treat population (ITT): includes all randomized subjects.
- Safety population: includes all randomized subjects who received study medication.
- Per-Protocol population: excludes patients with a major protocol violation from the analysis.

3.2.2.3 Analysis Methods

The primary efficacy analyses in both studies were conducted using eye as a unit of analysis. The mean difference between the K-Lens treated eyes and placebo treated eyes was compared using a 2-sample t-test. For subjects with missing ocular itching data, the last observation carried forward (LOCF) approach within a visit was used. As sensitivity analysis, the Applicant also conducted the analysis of the primary efficacy endpoint on the ITT population with missing data imputed using a multiple imputations (MI) approach.

The Applicant conducted the analysis of the continuous secondary efficacy endpoints using the 2-sample t-test. Qualitative endpoints were analyzed using Fisher's exact test or a chi-square test, as appropriate. The secondary efficacy variables were analyzed for the ITT population using observed data only.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patient Disposition

The disposition of all randomized subjects and reasons for premature study discontinuation are presented in Table 6. The proportion of subjects who discontinued study early ranged from 2.4% to 7.5% across all treatment groups of the two studies. In Study CR-4483, "subject choice" was reported as the most common reason for premature discontinuation across treatment groups while "Other" was the commonly reported reason for study discontinuation in Study CR-4484.

The "Other" category for the subject in Study CR-4483 refers to reduced visual acuity. In study CR-4484, for 1 subject in the placebo/placebo group and 1 of the 2 subjects in the K-Lens/K-Lens group "Other" refers to a hyperemia score ≥ 2.0 in any vessel bed or any ocular itching in either eye. For the second subject in the K-Lens/K-Lens group, " Other" refers to conjunctiva. One subject in the K-Lens/K-Lens group discontinued from Study CR-4484 due to a pregnancy related adverse event.

Table 6: Subject Disposition (All Randomized)

	Study CR-4483			
	Placebo/Placebo N=40	**K-Lens/Placebo N=41**	**K-Lens/K-Lens N=39**	**Overall N=120**
All Randomized	40 (100)	41 (100)	39 (100)	120 (100)
Completed Study	37 (92.5)	39 (95.1)	37 (94.9)	113 (94.2)
Discontinued Study	3 (7.5)	2 (4.9)	2 (5.1)	7 (5.8)
Reason for Study Discontinuation				
Subject Choice	3 (7.5)	1 (2.4)	2 (5.1)	6 (5.0)
Lost to follow up	0	0	0	0
Adverse Event	0	0	0	0
Death	0	0	0	0
Other	0	1 (2.4)	0	1 (0.8)
	Study CR-4484			
	Placebo/Placebo N=42	**K-Lens/Placebo N=41**	**K-Lens/K-Lens N=41**	**Overall N=124**
All Randomized	42 (100)	41 (100)	41 (100)	124 (100)
Completed Study	41 (97.6)	40 (97.6)	38 (92.7)	119 (96.0)
Discontinued Study	1 (2.4)	1 (2.4)	3 (7.3)	5 (4.0)
Reason for Study Discontinuation				
Subject Choice	0	0	0	0
Lost to follow up	0	1 (2.4)	0	1 (0.8)
Adverse Event	0	0	1 (2.4)	1 (0.8)
Death	0	0	0	0
Other	1 (2.4)	0	2 (4.9)	3 (2.4)

Source: Table 2 of the Applicant's Study Reports.

The number of subjects included in the different analysis populations is presented in Table 7. In both studies, more subjects were excluded from the per-protocol population (PP) in the two arms where at least one eye received K-Lens compared to the subjects who received placebo in both eyes. The main reason subjects were excluded from the PP population was due to incidences of missing itching scores at Visit 4 or 5.

Table 7: Summary of Analysis Populations

	Study CR-4483			
	Placebo/Placebo N=40	**K-Lens/Placebo N=41**	**K-Lens/K-Lens N=39**	**Overall N=120**
ITT population	40 (100)	41 (100)	39 (100)	120 (100)
Safety Population	40 (100)	41 (100)	39 (100)	120 (100)
Per Protocol Population	36 (90)	37 (97.2)	37 (94.9)	110 (91.7)
	Study CR-4484			
	Placebo/Placebo N=42	**K-Lens/Placebo N=41**	**K-Lens/K-Lens N=41**	**Overall N=124**
ITT population	42 (100)	41 (100)	41 (100)	124 (100)
Safety Population	42 (100)	41 (100)	41 (100)	124 (100)
Per Protocol Population	41 (97.6)	38 (92.7)	37 (90.2)	116 (93.5)

Source: Table 8 of the Applicant's Study Reports. ITT: Intent-to-treat

3.2.3.2 Demographic and Baseline Characteristics

There were no significant imbalances between the three arms in the demographics of age, gender, and race (Table 8 and Table 9). However, in both studies, there were more subjects with brown iris color in the K-Lens/K-Lens group compared to the other two arms (placebo/placebo and K-Lens/placebo). Except in the K-Lens/placebo group in Study CR-4483, there were more female participants than male participants. Subjects were predominantly white, of non-Hispanic ethnicity, with a mean age of around 29 years. Black subjects appear to be severely under-represented; especially in Study CR-4484, where none of the study participants were Black.

Table 8: Baseline and Demographic Characteristics (Study CR-4483)

	Treatment Groups			Overall N=120
	Placebo/Placebo N=40	K-Lens/Placebo N=41	K-Lens/K-Lens N=39	
Age (mean years ±SD) (Minimum, Maximum)	29±10.42 (15,56)	28.3±7.3 (12, 49)	29.5±8.43 (16, 54)	28.9±8.74 (12, 56)
Sex n (%)				
Female	21 (52.5)	19 (46.3)	21 (53.8)	61 (50.8)
Male	19 (47.5)	22 (53.7)	18 (46.2)	59 (49.2)
Race n (%)				
Caucasian	21 (52.5)	21 (51.2)	17 (43.6)	59 (49.2)
Asian	14 (35.0)	14 (34.1)	15 (38.5)	43 (35.8)
African American	4 (10.0)	4 (9.8)	5 (12.8)	13 (10.8)
American Indian or Alaskan Native	1 (2.5)	1 (2.4)	1 (2.6)	3 (2.5)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other	0	0	1 (2.6)	1 (0.8)
Ethnicity n (%)				
Non-Hispanic	40 (100)	40 (97.6)	38 (97.4)	118 (98.3)
Hispanic	0	1 (2.4)	1 (2.6)	2 (1.7)
Iris Color n (%)				
Brown	22 (55.0)	25 (61.0)	30 (76.9)	77 (64.2)
Blue	9 (22.5)	7 (17.1)	5 (12.8)	21 (17.5)
Hazel	3 (7.5)	6 (14.6)	4 (10.3)	13 (10.8)
Green	6 (15.0)	3 (7.3)	0	9 (7.5)

Source: Table 3 of the Applicant's Study Reports.

Table 9: Baseline and Demographic Characteristics (Study CR-4484)

	Treatment Groups			Overall N=124
	Placebo/Placebo N=42	K-Lens/Placebo N=41	K-Lens/K-Lens N=41	
Age (mean years ±SD) (Minimum, Maximum)	29.6±11.61 (13, 61)	29.4±12.86 (13, 57)	29.7±11.4 (13, 60)	29.6±11.87 (13, 61)
Sex n (%)				
Female	26 (61.9)	23 (56.1)	25 (61.0)	74 (59.7)
Male	16 (38.1)	18 (43.9)	16 (39.0)	50 (40.3)
Race n (%)				
Caucasian	30 (71.4)	31 (75.1)	30 (73.2)	91 (73.4)
Asian	11 (26.2)	9 (22.0)	10 (24.4)	30 (24.2)
African American	0	0	0	0

American Indian or Alaskan Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (2.4)	0	0	0
Other	1 (2.4)	1 (2.4)	1 (2.4)	3 (2.4)
Ethnicity n (%)				
Non-Hispanic	40 (95.2)	39 (95.1)	39 (95.1)	118 (95.2)
Hispanic	2 (4.8)	2 (4.9)	2 (4.9)	6 (4.8)
Iris Color n (%)				
Brown	19 (45.2)	18 (43.9)	22 (53.7)	59 (47.6)
Blue	13 (31.1)	13 (31.7)	8 (19.5)	34 (27.4)
Hazel	5 (11.9)	4 (9.8)	7 (17.1)	16 (12.9)
Green	5 (11.9)	5 (12.2)	4 (9.8)	14 (11.3)
Other	0	1 (2.4)	0	1 (0.8)

Source: Table 3 of the Applicant's Study Reports.

3.2.4 Results and Conclusions

3.2.4.1 Efficacy Results

Primary Efficacy Analysis

Recall that the primary efficacy endpoint is the mean itching score at each of the 6 timepoints (3, 5, 7 minutes post-CAC at Visits 4 and 5); and evaluated in the ITT population for the primary analysis. Per the study protocols, efficacy at either Visit 4 and Visit 5 is demonstrated if a superiority of K-Lens over vehicle is demonstrated by at least 0.5 units for all time points tested at that visit and by at least 1 unit for the majority of time points.

The Applicant's primary efficacy analyses results are shown in Table 10 and Table 11. For both studies, there was a statistically significant difference between K-Lens treated eyes and placebo-treated eyes at each of the 6 timepoints. The treatment differences ranged between 1.05 to 1.38 in favor of the K-Lens treated eyes. Therefore, the results in both studies support the efficacy criteria.

Table 10: Primary Efficacy Endpoint Summary (Study CR-4483: ITT)

	K-lens	Placebo		
Visit (Time)	Mean (StdDev)	Mean (StdDev)		Diff(95% CI)
Day 0 (3 Min)	0.61(0.7)	1.71(0.89)		-1.1 (-1.31,-0.9)
Day 0 (5 Min)	0.74(0.73)	1.96(0.9)		-1.22 (-1.43,-1.01)
Day 0 (7 Min)	0.79(0.79)	1.86(0.94)		-1.07 (-1.29,-0.85)
Day 14 (3 Min)	0.42(0.66)	1.6(0.87)		-1.18 (-1.39,-0.98)
Day 14 (5 Min)	0.56(0.71)	1.82(0.91)		-1.26 (-1.47,-1.04)
Day 14 (7 Min)	0.54(0.7)	1.69(0.95)		-1.15 (-1.37,-0.93)

Source: Adapted from Table 10 of the Applicant's Study Reports.

Table 11: Primary Efficacy Endpoint Summary (Study CR-4484: ITT)

	K-lens	Placebo		
Visit (Time)	Mean (StdDev)	Mean (StdDev)		Diff(95% CI)
Day 0 (3 Min)	0.75(0.83)	1.8(0.89)		-1.05 (-1.27,-0.83)
Day 0 (5 Min)	0.88(0.91)	2.04(0.88)		-1.16 (-1.38,-0.93)
Day 0 (7 Min)	0.86(0.91)	1.99(0.89)		-1.13 (-1.35,-0.9)
Day 14 (3 Min)	0.42(0.61)	1.72(0.94)		-1.3 (-1.5,-1.09)
Day 14 (5 Min)	0.56(0.72)	1.94(0.91)		-1.38 (-1.59,-1.17)
Day 14 (7 Min)	0.59(0.8)	1.83(0.98)		-1.24 (-1.47,-1.01)

Source: Adapted from Table 10 of the Applicant's Study Reports.

Sensitivity Analyses

To assess the robustness of the results of the primary efficacy analyses, both the reviewer and the Applicant conducted sensitivity analyses. This section summarizes the results of these analyses. The results from these analyses are overall consistent with the primary efficacy analysis findings.

A. Applicant's Sensitivity Analyses

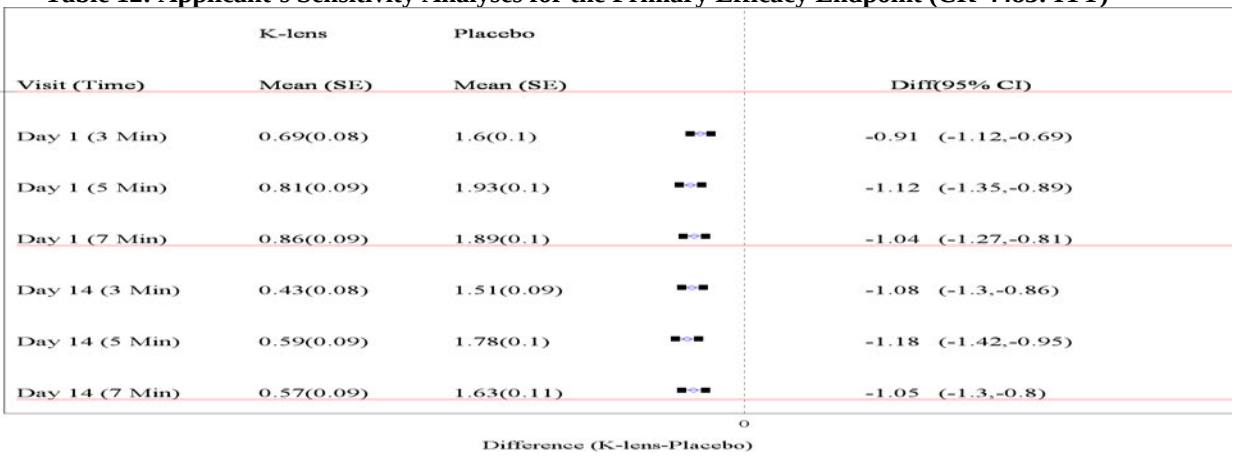
i. Accounting for correlation between eyes

The Applicant's primary efficacy analysis was conducted based on a 2-sample t-test for each of the six measurement times separately. This analysis ignores the possible correlation between eyes from the same subject and among measurements taken from the same subject over time. This could potentially result in biased estimates, as well as incorrect standard errors of the estimated treatment differences.

To account for possible correlation between outcomes collected from eyes from the same subject, the Applicant conducted the analysis of the primary efficacy endpoint using a mixed model for repeated measures (MMRM). The model included treatment, site, and treatment by site interaction as fixed effects. The correlation between eyes were assumed to be different for the three treatment groups (K-Lens/K-Lens, placebo/placebo, and K-Lens/placebo). This analysis provided results that are consistent with the primary efficacy analysis results and support the efficacy of K-Lens (Table 12 and Table 13).

Table 12: Applicant's Sensitivity Analyses for the Primary Efficacy Endpoint (CR-4483: ITT)

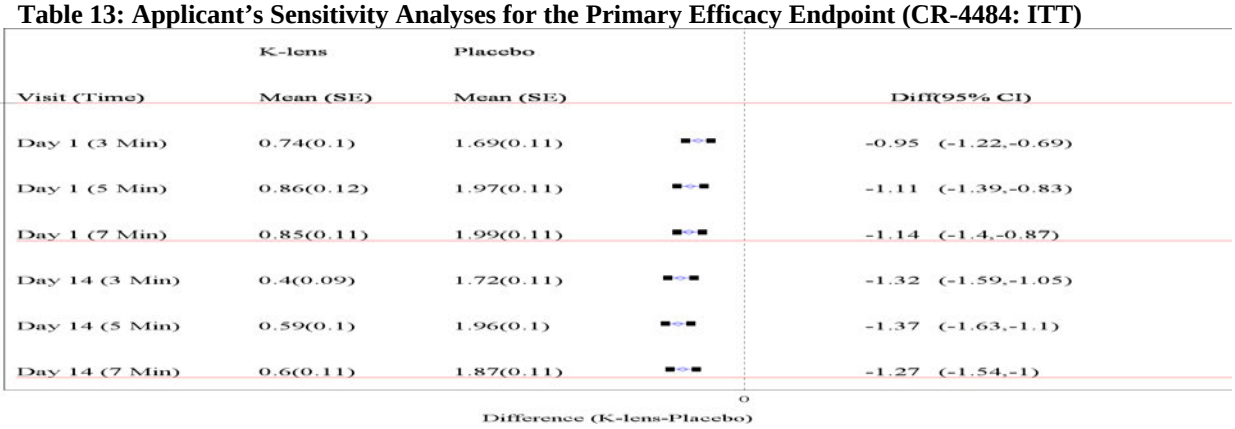
Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.69(0.08)	1.6(0.1)	-0.91 (-1.12,-0.69)
Day 1 (5 Min)	0.81(0.09)	1.93(0.1)	-1.12 (-1.35,-0.89)
Day 1 (7 Min)	0.86(0.09)	1.89(0.1)	-1.04 (-1.27,-0.81)
Day 14 (3 Min)	0.43(0.08)	1.51(0.09)	-1.08 (-1.3,-0.86)
Day 14 (5 Min)	0.59(0.09)	1.78(0.1)	-1.18 (-1.42,-0.95)
Day 14 (7 Min)	0.57(0.09)	1.63(0.11)	-1.05 (-1.3,-0.8)



Source: Adapted from Table TEFITX01 of the Applicant's Summary of Clinical Efficacy. The analysis is conducted using a MMRM.

Table 13: Applicant's Sensitivity Analyses for the Primary Efficacy Endpoint (CR-4484: ITT)

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.74(0.1)	1.69(0.11)	-0.95 (-1.22,-0.69)
Day 1 (5 Min)	0.86(0.12)	1.97(0.11)	-1.11 (-1.39,-0.83)
Day 1 (7 Min)	0.85(0.11)	1.99(0.11)	-1.14 (-1.4,-0.87)
Day 14 (3 Min)	0.4(0.09)	1.72(0.11)	-1.32 (-1.59,-1.05)
Day 14 (5 Min)	0.59(0.1)	1.96(0.1)	-1.37 (-1.63,-1.1)
Day 14 (7 Min)	0.6(0.11)	1.87(0.11)	-1.27 (-1.54,-1)



Source: Adapted from Table TEFITX02 of the Applicant's Summary of Clinical Efficacy. The analysis is conducted using a MMRM.

ii. Missing Data

There was very minimal missing data for the primary efficacy endpoint in both studies. The primary efficacy analysis used a LOCF approach to deal with missing data. As sensitivity analysis, the Applicant conducted a multiple imputation analysis. The results of this analysis are consistent with the primary efficacy analysis results.

B. Reviewer's Sensitivity Analyses

i. Correlation of outcomes between eyes and over time

The Applicant's sensitivity analysis accounted for the possible correlation between eyes from the same subject. However, outcomes taken overtime from the same eye are also potentially correlated. To evaluate the effect of ignoring this correlation on the efficacy results, the reviewer conducted the analysis of the primary efficacy endpoint by accounting for all possible sources of correlations. This analysis is conducted using an MMRM model. The model included treatment, time (3, 5 7 minutes at Visit 4 and 5), and the interaction of time and treatment. The unstructured correlation matrix was used to account for possible correlation between eyes from

the same subject and among measurements taken over time from a given eye. The results of this analysis are consistent with the Applicant's primary efficacy analysis findings (Table 14 and Table 15).

Table 14: Reviewer's Sensitivity Analyses for the Primary Efficacy Endpoint (CR-4483: ITT)

	K-lens	Placebo	
Visit (Time)	Mean (StdErr)	Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.72(0.08)	1.67(0.08)	-0.95 (-1.13,-0.77)
Day 0 (5 Min)	0.79(0.08)	1.91(0.08)	-1.12 (-1.31,-0.94)
Day 0 (7 Min)	0.81(0.08)	1.81(0.08)	-1 (-1.19,-0.8)
Day 14 (3 Min)	0.5(0.08)	1.59(0.08)	-1.1 (-1.28,-0.91)
Day 14 (5 Min)	0.57(0.08)	1.81(0.08)	-1.23 (-1.42,-1.05)
Day 14 (7 Min)	0.54(0.08)	1.65(0.08)	-1.11 (-1.3,-0.92)

Difference (K-lens-Placebo)

Table 15: Reviewer's Sensitivity Analyses for the Primary Efficacy Endpoint (CR-4484: ITT)

	K-lens	Placebo	
Visit (Time)	Mean (StdErr)	Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.82(0.08)	1.76(0.08)	-0.93 (-1.12,-0.75)
Day 0 (5 Min)	0.92(0.09)	1.98(0.09)	-1.06 (-1.26,-0.87)
Day 0 (7 Min)	0.88(0.09)	1.95(0.08)	-1.07 (-1.26,-0.87)
Day 14 (3 Min)	0.49(0.08)	1.67(0.08)	-1.18 (-1.37,-1)
Day 14 (5 Min)	0.58(0.08)	1.89(0.08)	-1.31 (-1.5,-1.12)
Day 14 (7 Min)	0.57(0.09)	1.81(0.09)	-1.24 (-1.44,-1.04)

Difference (K-lens-Placebo)

ii. Treatment comparison between K-Lens and Placebo within each randomized group

Recall that subjects were randomized to three treatment groups. In two of these groups, subjects received placebo in both eyes and K-Lens in both eyes, respectively. In the third group, subjects received placebo in one eye and K-Lens in the other.

The comparison between K-Lens wearing eyes and placebo-wearing eyes in the latter group is a within-subject comparison. On the other hand, in the two groups where subjects received the same treatment in both eyes, the treatment comparison is more like a between-group comparison. Consequently, it is possible that the effect of ignoring the correlation on the treatment differences might be different for the latter group compared to the two randomized groups where both eyes were treated using the same product. To this end, the reviewer first compared the K-Lens wearing eyes against placebo-lens wearing eyes based on data from the two randomized groups where subjects received the same treatment in both eyes, i.e., subjects who received K-Lens or placebo in both eyes. In addition, the placebo and K-Lens treated eyes

are also compared for subjects who received K-Lens in one eye and placebo in the other eye. These analyses are conducted using the MMRM model by accounting for between and within eye correlations. The results of this analysis are consistent with the Applicant's primary efficacy analysis findings (Table 16-Table 19).

Table 16: Reviewer's Sensitivity Analyses (CR-4483: K-Lens or placebo in both)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.54(0.11)	1.83(0.11)	-1.29 (-1.6,-0.97)
Day 0 (5 Min)	0.7(0.12)	2.06(0.12)	-1.36 (-1.69,-1.03)
Day 0 (7 Min)	0.77(0.13)	1.95(0.12)	-1.18 (-1.53,-0.83)
Day 14 (3 Min)	0.34(0.12)	1.67(0.12)	-1.33 (-1.67,-1)
Day 14 (5 Min)	0.51(0.12)	1.85(0.12)	-1.34 (-1.66,-1.01)
Day 14 (7 Min)	0.47(0.12)	1.71(0.12)	-1.23 (-1.55,-0.91)

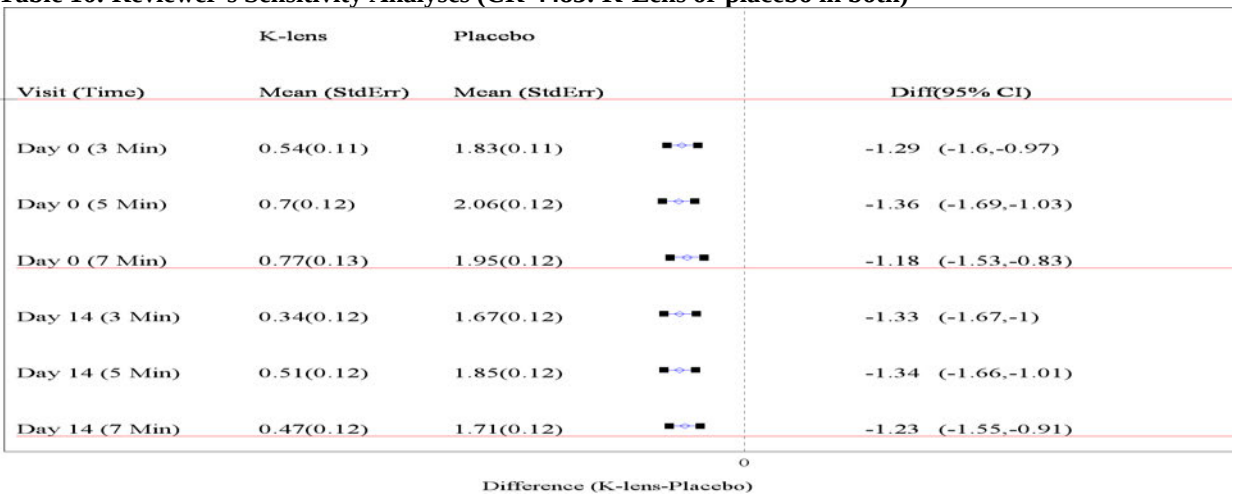


Table 17: Reviewer's Sensitivity Analyses (CR-4484: K-Lens or placebo in both)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.72(0.11)	1.9(0.11)	-1.18 (-1.48,-0.88)
Day 0 (5 Min)	0.91(0.12)	2.17(0.12)	-1.26 (-1.59,-0.93)
Day 0 (7 Min)	0.91(0.12)	2.11(0.12)	-1.19 (-1.52,-0.87)
Day 14 (3 Min)	0.36(0.1)	1.79(0.1)	-1.43 (-1.71,-1.15)
Day 14 (5 Min)	0.53(0.12)	2.01(0.12)	-1.48 (-1.8,-1.15)
Day 14 (7 Min)	0.58(0.13)	1.87(0.12)	-1.29 (-1.64,-0.94)

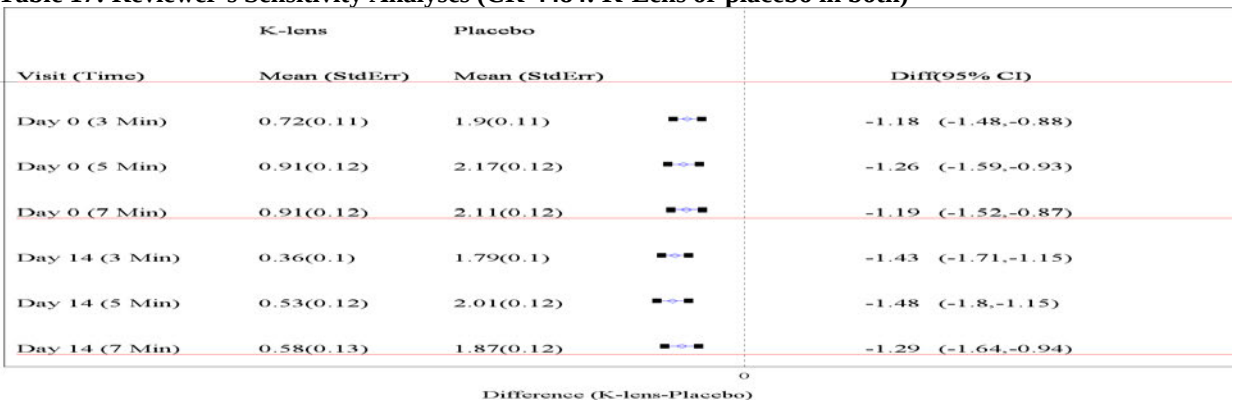


Table 18: Reviewer's Sensitivity Analyses (CR-4483: K-Lens in one placebo in the other)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.73(0.12)	1.51(0.12)	-0.78 (-1.04,-0.52)
Day 0 (5 Min)	0.83(0.12)	1.84(0.12)	-1.01 (-1.28,-0.74)
Day 0 (7 Min)	0.82(0.13)	1.73(0.13)	-0.91 (-1.18,-0.63)
Day 14 (3 Min)	0.53(0.13)	1.53(0.13)	-0.99 (-1.27,-0.72)
Day 14 (5 Min)	0.64(0.13)	1.83(0.13)	-1.19 (-1.47,-0.92)
Day 14 (7 Min)	0.63(0.13)	1.68(0.13)	-1.05 (-1.34,-0.76)

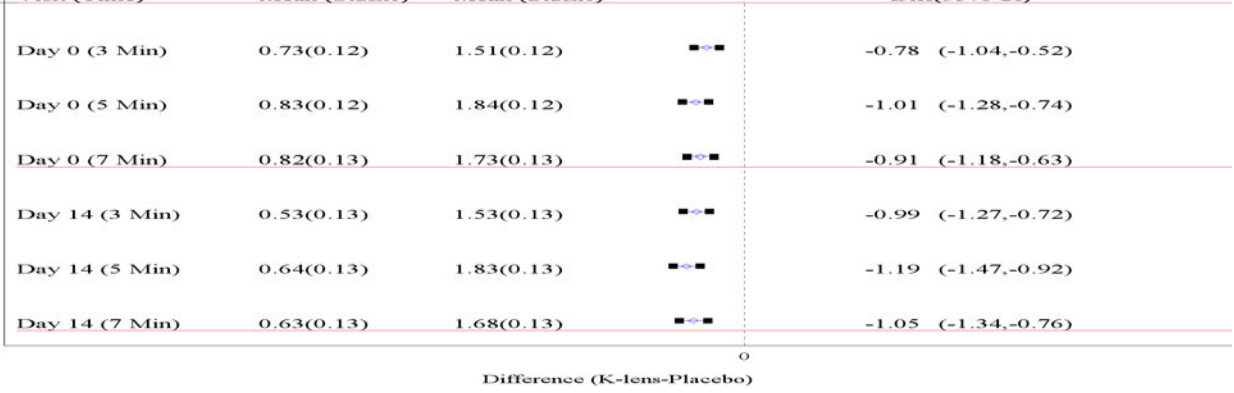
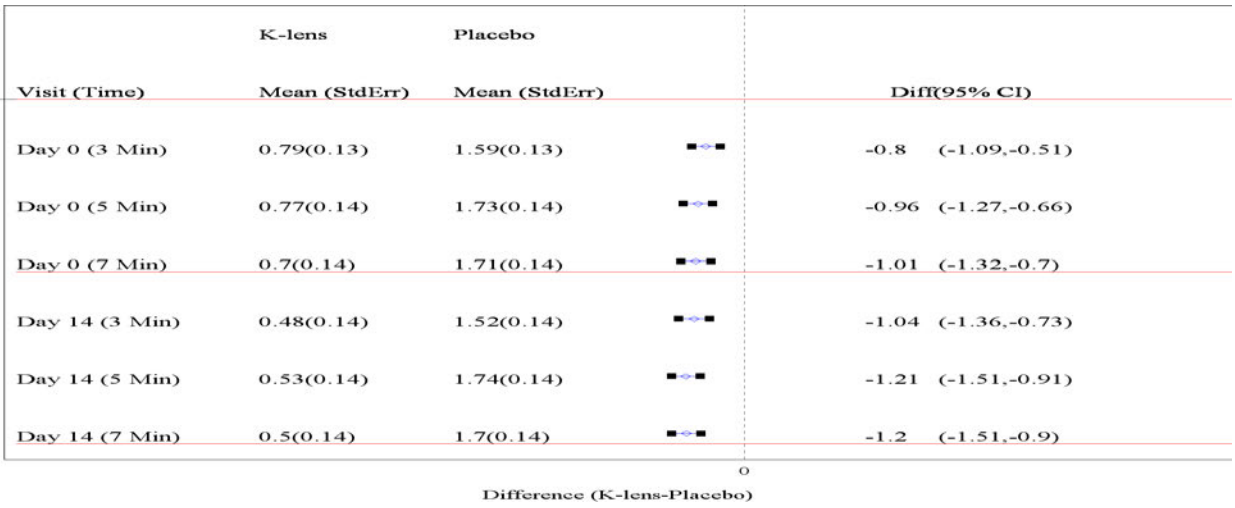


Table 19: Reviewer's Sensitivity Analyses (CR-4484: K-Lens in one placebo in the other)

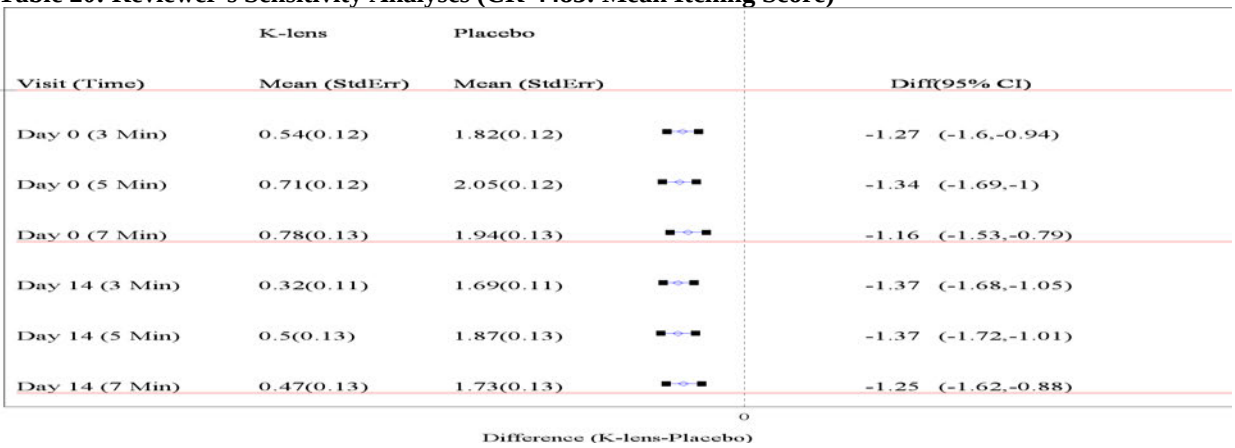


Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.79(0.13)	1.59(0.13)	-0.8 (-1.09,-0.51)
Day 0 (5 Min)	0.77(0.14)	1.73(0.14)	-0.96 (-1.27,-0.66)
Day 0 (7 Min)	0.7(0.14)	1.71(0.14)	-1.01 (-1.32,-0.7)
Day 14 (3 Min)	0.48(0.14)	1.52(0.14)	-1.04 (-1.36,-0.73)
Day 14 (5 Min)	0.53(0.14)	1.74(0.14)	-1.21 (-1.51,-0.91)
Day 14 (7 Min)	0.5(0.14)	1.7(0.14)	-1.2 (-1.51,-0.9)

iii. Subject as a unit of analysis

In the analyses presented in the previous sections and conducted by both the reviewer and the Applicant, the eye was used as a unit of analysis. This reviewer conducted the analysis of the primary efficacy endpoint by using the subject as the unit of analysis. In this analysis, the itching score from each subject is summarized using the mean, minimum and maximum itching scores from the two eyes. The summaries for the K-Lens treated eyes are then compared to the placebo-treated eyes. This analysis is conducted based on data from the two randomized groups where subjects have received the same treatment in both eyes. The analysis accounts for possible correlation in outcomes over time using a MMRM with an unstructured correlation matrix. The results for this analysis are also consistently favorable to the K-Lens treated eyes (Table 20- Table 25).

Table 20: Reviewer's Sensitivity Analyses (CR-4483: Mean Itching Score)



Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.54(0.12)	1.82(0.12)	-1.27 (-1.6,-0.94)
Day 0 (5 Min)	0.71(0.12)	2.05(0.12)	-1.34 (-1.69,-1)
Day 0 (7 Min)	0.78(0.13)	1.94(0.13)	-1.16 (-1.53,-0.79)
Day 14 (3 Min)	0.32(0.11)	1.69(0.11)	-1.37 (-1.68,-1.05)
Day 14 (5 Min)	0.5(0.13)	1.87(0.13)	-1.37 (-1.72,-1.01)
Day 14 (7 Min)	0.47(0.13)	1.73(0.13)	-1.25 (-1.62,-0.88)

Table 21: Reviewer's Sensitivity Analyses (CR-4484: Mean Itching Score)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.72(0.13)	1.89(0.13)	-1.17 (-1.54,-0.81)
Day 0 (5 Min)	0.91(0.13)	2.17(0.13)	-1.26 (-1.62,-0.89)
Day 0 (7 Min)	0.91(0.13)	2.11(0.13)	-1.19 (-1.55,-0.84)
Day 14 (3 Min)	0.37(0.11)	1.8(0.11)	-1.44 (-1.75,-1.12)
Day 14 (5 Min)	0.53(0.12)	2.02(0.12)	-1.49 (-1.82,-1.16)
Day 14 (7 Min)	0.57(0.14)	1.88(0.13)	-1.31 (-1.69,-0.92)

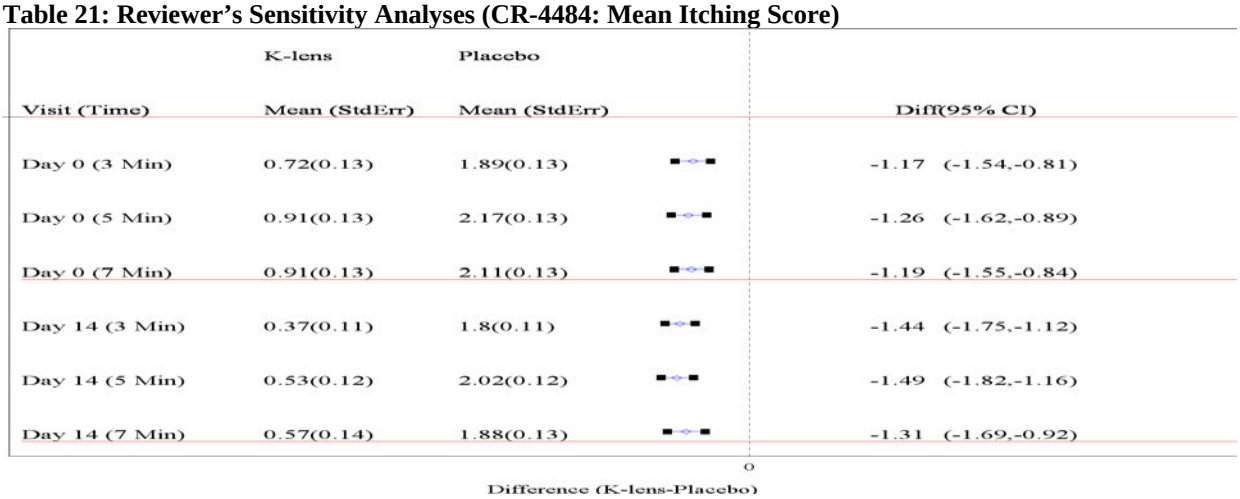


Table 22: Reviewer's Sensitivity Analyses (CR-4483: Minimum Itching Score)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.41(0.12)	1.59(0.12)	-1.18 (-1.52,-0.83)
Day 0 (5 Min)	0.55(0.13)	1.84(0.13)	-1.29 (-1.66,-0.91)
Day 0 (7 Min)	0.63(0.14)	1.76(0.14)	-1.13 (-1.54,-0.73)
Day 14 (3 Min)	0.27(0.12)	1.42(0.12)	-1.15 (-1.49,-0.8)
Day 14 (5 Min)	0.39(0.14)	1.7(0.14)	-1.3 (-1.7,-0.91)
Day 14 (7 Min)	0.37(0.14)	1.59(0.14)	-1.22 (-1.62,-0.81)

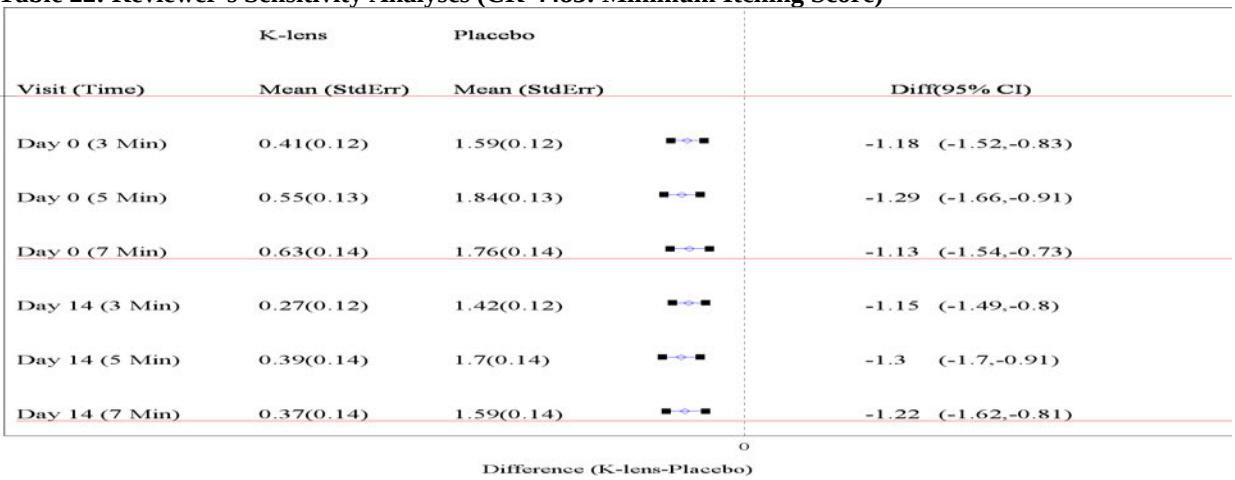


Table 23: Reviewer's Sensitivity Analyses (CR-4484: Minimum Itching Score)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.63(0.14)	1.74(0.14)	-1.1 (-1.5,-0.71)
Day 0 (5 Min)	0.74(0.15)	2.01(0.14)	-1.27 (-1.68,-0.86)
Day 0 (7 Min)	0.73(0.14)	1.93(0.14)	-1.2 (-1.58,-0.81)
Day 14 (3 Min)	0.27(0.12)	1.61(0.12)	-1.34 (-1.68,-1.01)
Day 14 (5 Min)	0.35(0.13)	1.81(0.12)	-1.46 (-1.81,-1.11)
Day 14 (7 Min)	0.4(0.14)	1.71(0.14)	-1.31 (-1.71,-0.91)

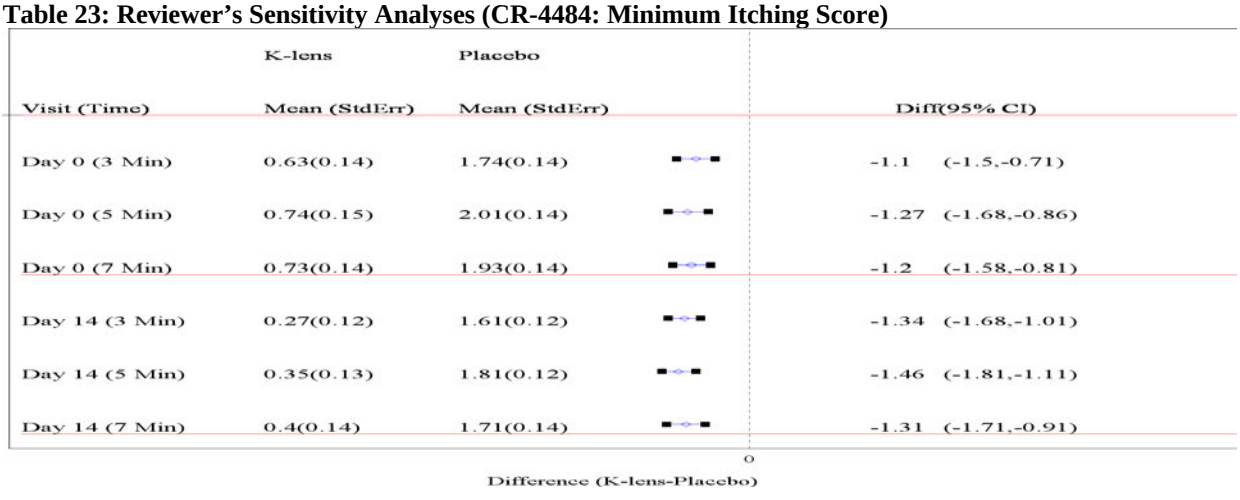


Table 24: Reviewer's Sensitivity Analyses (CR-4483: Maximum Itching Score)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.68(0.12)	2.05(0.12)	-1.37 (-1.72,-1.02)
Day 0 (5 Min)	0.86(0.13)	2.26(0.12)	-1.4 (-1.76,-1.05)
Day 0 (7 Min)	0.94(0.13)	2.13(0.13)	-1.19 (-1.56,-0.81)
Day 14 (3 Min)	0.38(0.12)	1.96(0.12)	-1.58 (-1.92,-1.25)
Day 14 (5 Min)	0.61(0.12)	2.04(0.12)	-1.43 (-1.78,-1.08)
Day 14 (7 Min)	0.57(0.13)	1.86(0.13)	-1.29 (-1.66,-0.93)

Table 25: Reviewer's Sensitivity Analyses (CR-4484: Maximum Itching Score)

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.8(0.13)	2.05(0.12)	-1.24 (-1.59,-0.89)
Day 0 (5 Min)	1.09(0.13)	2.33(0.12)	-1.25 (-1.6,-0.9)
Day 0 (7 Min)	1.1(0.13)	2.29(0.13)	-1.19 (-1.55,-0.83)
Day 14 (3 Min)	0.46(0.11)	1.99(0.11)	-1.53 (-1.85,-1.21)
Day 14 (5 Min)	0.71(0.13)	2.22(0.12)	-1.51 (-1.87,-1.16)
Day 14 (7 Min)	0.75(0.15)	2.04(0.14)	-1.3 (-1.71,-0.88)

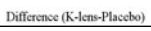
iv. Analysis by Site in Study CR-4483

Per the Applicant, the pivotal efficacy study CR-4483, had 2 sites, Site 1 (Eugene B. McLaurin, MD) and Site 2 (Fred Kurata, MD). They state that, during a post-study assessment, it was discovered that the test article shipment sheet and study/site reconciliation worksheet inadvertently contained manufacturing lot information that identified the active (" K-Lens ") and placebo test articles and was shipped to Site 1. Consequently, the CR-4483 Clinical Study Report (CSR) was amended to include a site by treatment interaction data analysis. Per the Applicant's results, the interaction term was not statistically significant. Based on this, the Applicant concluded that, the disclosure did not affect the treatment comparisons. The reviewer's analysis of the primary efficacy endpoint accounting for all possible correlation for each site separately provides similar conclusion of efficacy for K-Lens. However, the magnitude of the observed treatment differences in Site 1 are more favorable to the K-lens arm than those observed in Site 2 (Table 26).

Table 26: Analyses for the Primary Efficacy Endpoint by Site (CR-4483: ITT)

Site 1

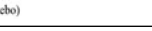
Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.6(0.09)	1.64(0.09)	-1.04 (-1.27,-0.82)
Day 0 (5 Min)	0.71(0.1)	1.89(0.1)	-1.19 (-1.43,-0.95)
Day 0 (7 Min)	0.72(0.1)	1.7(0.1)	-0.99 (-1.23,-0.74)
Day 14 (3 Min)	0.41(0.1)	1.7(0.1)	-1.29 (-1.53,-1.05)
Day 14 (5 Min)	0.5(0.1)	1.86(0.1)	-1.35 (-1.59,-1.11)
Day 14 (7 Min)	0.47(0.1)	1.7(0.1)	-1.23 (-1.47,-0.99)



Difference (K-lens-Placebo)

Site 2

Visit (Time)	K-lens Mean (StdErr)	Placebo Mean (StdErr)	Diff(95% CI)
Day 0 (3 Min)	0.94(0.14)	1.69(0.14)	-0.75 (-1.03,-0.47)
Day 0 (5 Min)	0.97(0.15)	1.93(0.15)	-0.96 (-1.25,-0.67)
Day 0 (7 Min)	1.05(0.15)	1.96(0.15)	-0.91 (-1.2,-0.61)
Day 14 (3 Min)	0.69(0.13)	1.34(0.13)	-0.65 (-0.9,-0.39)
Day 14 (5 Min)	0.79(0.13)	1.63(0.13)	-0.84 (-1.1,-0.58)
Day 14 (7 Min)	0.76(0.14)	1.46(0.14)	-0.7 (-0.97,-0.43)



Difference (K-lens-Placebo)

Source: Reviewer's Analysis

Analysis of Secondary Efficacy Endpoints

Recall, the two studies evaluated the following secondary efficacy endpoints at 7, 15, and, 20 minutes post CAC at Visits 4 and 5:

1. Ciliary hyperemia
2. Conjunctival hyperemia
3. Episcleral hyperemia
4. Chemosis
5. Lid swelling
6. Mucous discharge
7. Tearing

Also recall that, outcomes #1-#4 were evaluated by the investigator using a 0.5 increment scale where 0 = none and 4.0 = extremely severe. Outcome 5 was evaluated by the subject using a 4-point scale where 0 = none and 3 = severe). Outcomes 6 and 7 were evaluated by the subject as Absent and Present.

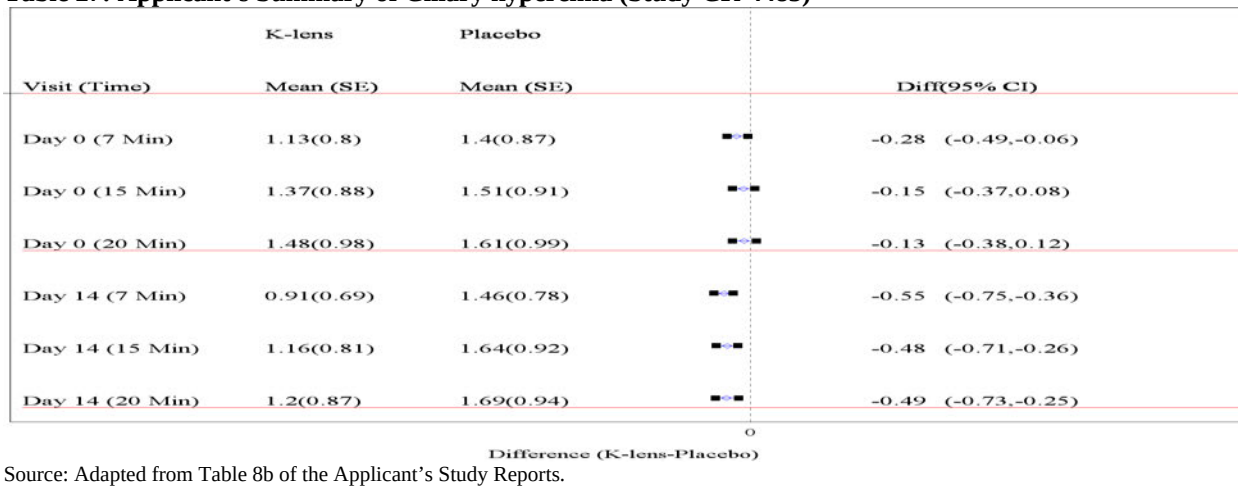
The results for the secondary efficacy endpoints are presented in Table 27-Table 38. Note, similar to the primary efficacy endpoint, for secondary efficacy endpoints measured on the 0-4 scales, K-Lens was to be declared superior to the placebo lens if the treatment differences are at least 0.5. Based on the reported results, the clinical requirements are not met in either study. However, the results are consistently numerically favorable to the K-lens treated eyes. Also note, because multiplicity adjustment was not pre-specified for the secondary efficacy endpoints, formal inferential claim for these endpoints could not be made. Therefore, the results of the secondary efficacy endpoint could only be viewed as exploratory.

Reviewer's remark: Similar to the primary efficacy analysis, the Applicant's analysis of the continuous secondary efficacy endpoints was based on a 2-sample t-test and did not account for the possible correlation in outcomes from two eyes of the same subject or among outcomes measured over time from the same eye. This reviewer conducted additional analyses accounting for these possible sources of correlations. The results are consistent with the Applicant's findings.

Reviewer's remark: Summary for the mucous discharge is not presented because mucous discharge was noted for very few subjects in both arms. For example, in Study CR-4483, only 2 eyes, both in the K-Lens group, had mucous discharge at 7 minutes post CAC challenge.

Table 27: Applicant's Summary of Ciliary hyperemia (Study CR-4483)

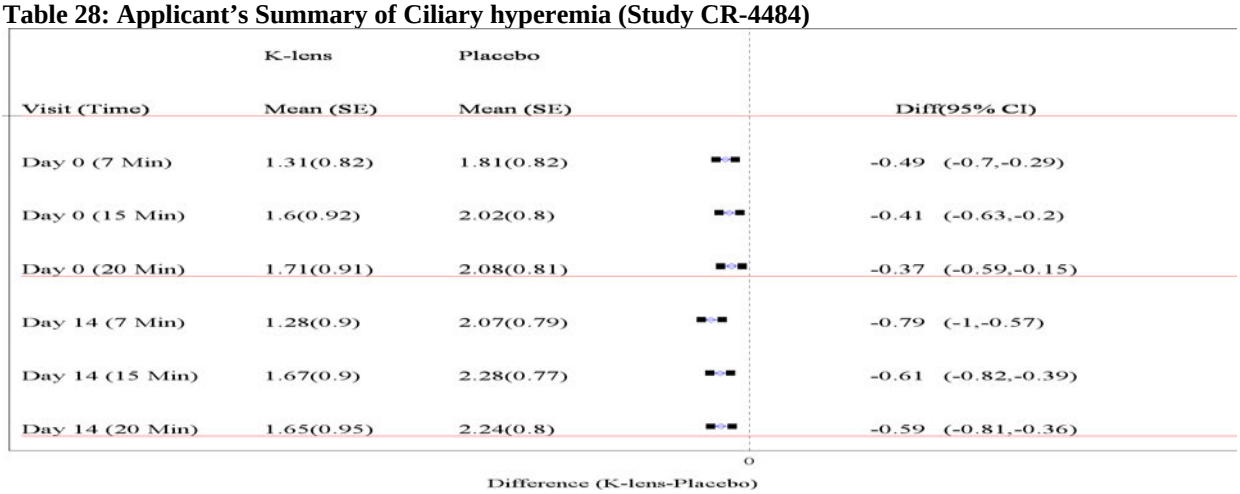
	K-lens	Placebo	
Visit (Time)	Mean (SE)	Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	1.13(0.8)	1.4(0.87)	-0.28 (-0.49,-0.06)
Day 0 (15 Min)	1.37(0.88)	1.51(0.91)	-0.15 (-0.37,0.08)
Day 0 (20 Min)	1.48(0.98)	1.61(0.99)	-0.13 (-0.38,0.12)
Day 14 (7 Min)	0.91(0.69)	1.46(0.78)	-0.55 (-0.75,-0.36)
Day 14 (15 Min)	1.16(0.81)	1.64(0.92)	-0.48 (-0.71,-0.26)
Day 14 (20 Min)	1.2(0.87)	1.69(0.94)	-0.49 (-0.73,-0.25)



Source: Adapted from Table 8b of the Applicant's Study Reports.

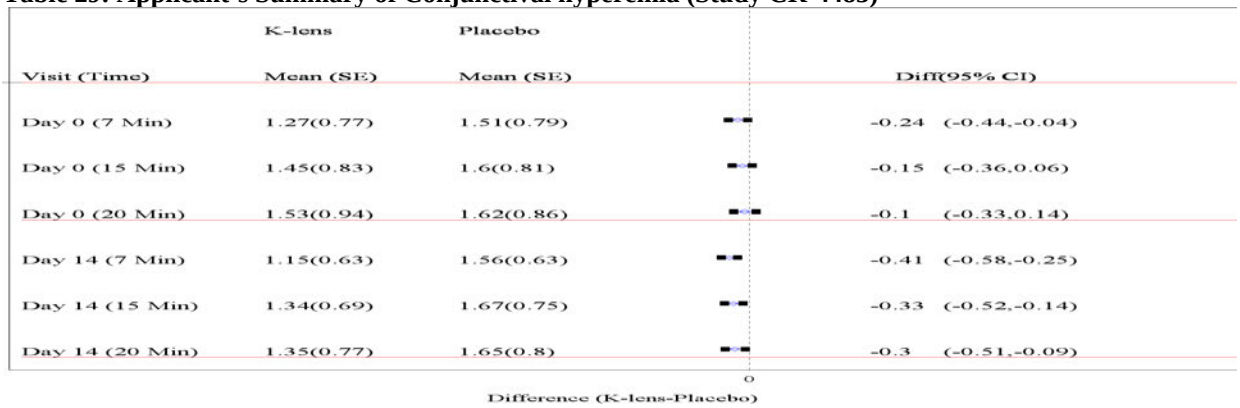
Table 28: Applicant's Summary of Ciliary hyperemia (Study CR-4484)

	K-lens	Placebo	
Visit (Time)	Mean (SE)	Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	1.31(0.82)	1.81(0.82)	-0.49 (-0.7,-0.29)
Day 0 (15 Min)	1.6(0.92)	2.02(0.8)	-0.41 (-0.63,-0.2)
Day 0 (20 Min)	1.71(0.91)	2.08(0.81)	-0.37 (-0.59,-0.15)
Day 14 (7 Min)	1.28(0.9)	2.07(0.79)	-0.79 (-1,-0.57)
Day 14 (15 Min)	1.67(0.9)	2.28(0.77)	-0.61 (-0.82,-0.39)
Day 14 (20 Min)	1.65(0.95)	2.24(0.8)	-0.59 (-0.81,-0.36)



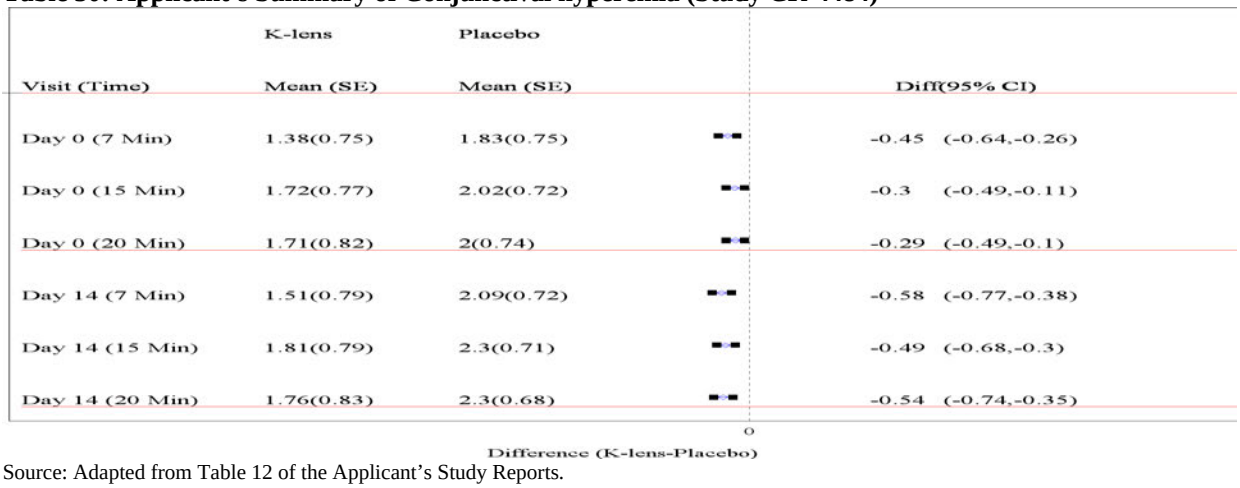
Source: Adapted from Table 8b of the Applicant's Study Reports.

Table 29: Applicant's Summary of Conjunctival hyperemia (Study CR-4483)



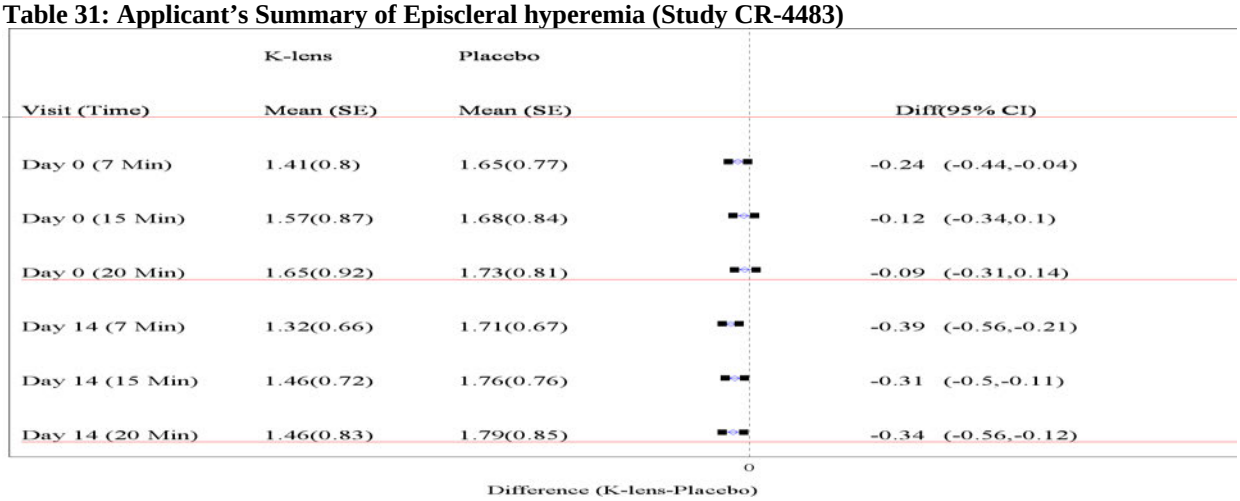
Source: Adapted from Table 12 of the Applicant's Study Reports.

Table 30: Applicant's Summary of Conjunctival hyperemia (Study CR-4484)



Source: Adapted from Table 12 of the Applicant's Study Reports.

Table 31: Applicant's Summary of Episcleral hyperemia (Study CR-4483)



Source: Adapted from Table 13 of the Applicant's Study Reports.

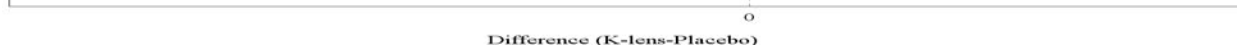
Table 32: Applicant's Summary of Episcleral hyperemia (Study CR-4484)

	K-lens	Placebo	
Visit (Time)	Mean (SE)	Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	1.44(0.84)	1.87(0.76)	-0.43 (-0.63,-0.23)
Day 0 (15 Min)	1.76(0.87)	2.05(0.69)	-0.3 (-0.49,-0.1)
Day 0 (20 Min)	1.82(0.88)	2.09(0.7)	-0.27 (-0.47,-0.07)
Day 14 (7 Min)	1.48(0.88)	2.13(0.78)	-0.65 (-0.86,-0.43)
Day 14 (15 Min)	1.88(0.83)	2.36(0.76)	-0.48 (-0.68,-0.27)
Day 14 (20 Min)	1.86(0.84)	2.38(0.73)	-0.52 (-0.72,-0.32)

Source: Adapted from Table 13 of the Applicant's Study Reports.

Table 33: Applicant's Summary of Chemosis (Study CR-4483)

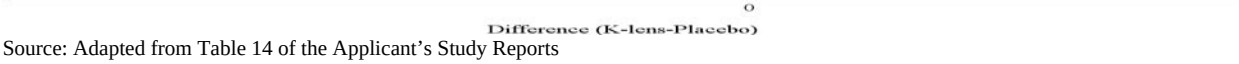
	K-lens	Placebo	
Visit (Time)	Mean (SE)	Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	0.19(0.34)	0.41(0.52)	-0.22 (-0.33,-0.11)
Day 0 (15 Min)	0.36(0.56)	0.42(0.62)	-0.06 (-0.21,0.09)
Day 0 (20 Min)	0.38(0.57)	0.47(0.66)	-0.09 (-0.25,0.07)
Day 14 (7 Min)	0.18(0.28)	0.43(0.41)	-0.25 (-0.34,-0.16)
Day 14 (15 Min)	0.32(0.38)	0.67(0.58)	-0.35 (-0.48,-0.22)
Day 14 (20 Min)	0.34(0.4)	0.66(0.67)	-0.32 (-0.47,-0.17)



Source: Adapted from Table 14 of the Applicant's Study Reports

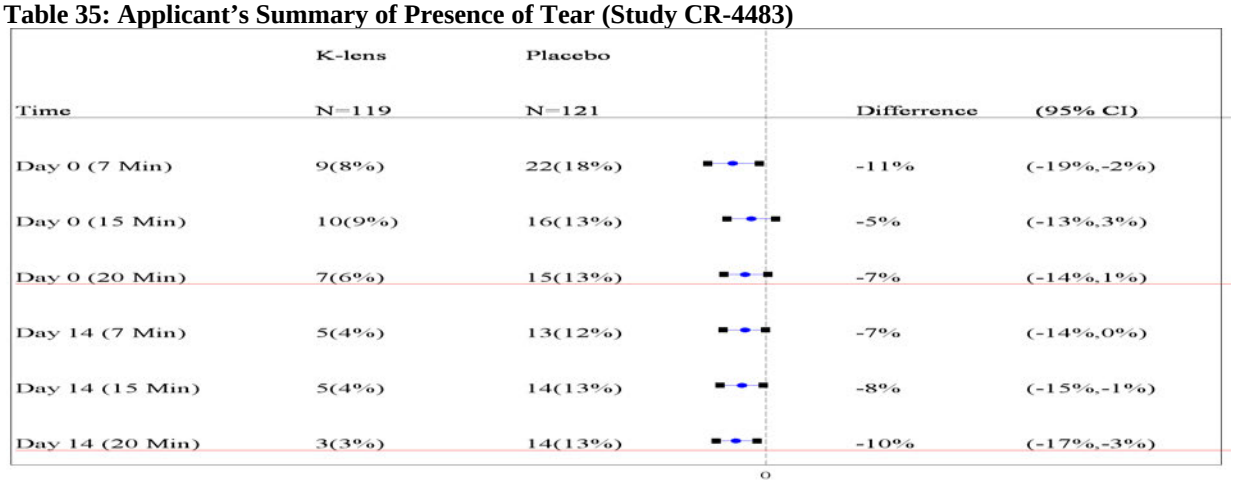
Table 34: Applicant's Summary of Chemosis (Study CR-4484)

	K-lens	Placebo	
Visit (Time)	Mean (SE)	Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	0.32(0.34)	0.52(0.55)	-0.2 (-0.31,-0.08)
Day 0 (15 Min)	0.54(0.55)	0.73(0.7)	-0.19 (-0.35,-0.03)
Day 0 (20 Min)	0.58(0.6)	0.77(0.74)	-0.2 (-0.36,-0.03)
Day 14 (7 Min)	0.38(0.5)	0.71(0.72)	-0.33 (-0.49,-0.17)
Day 14 (15 Min)	0.57(0.64)	0.96(0.84)	-0.39 (-0.58,-0.2)
Day 14 (20 Min)	0.59(0.76)	1(0.87)	-0.41 (-0.62,-0.2)



Source: Adapted from Table 14 of the Applicant's Study Reports

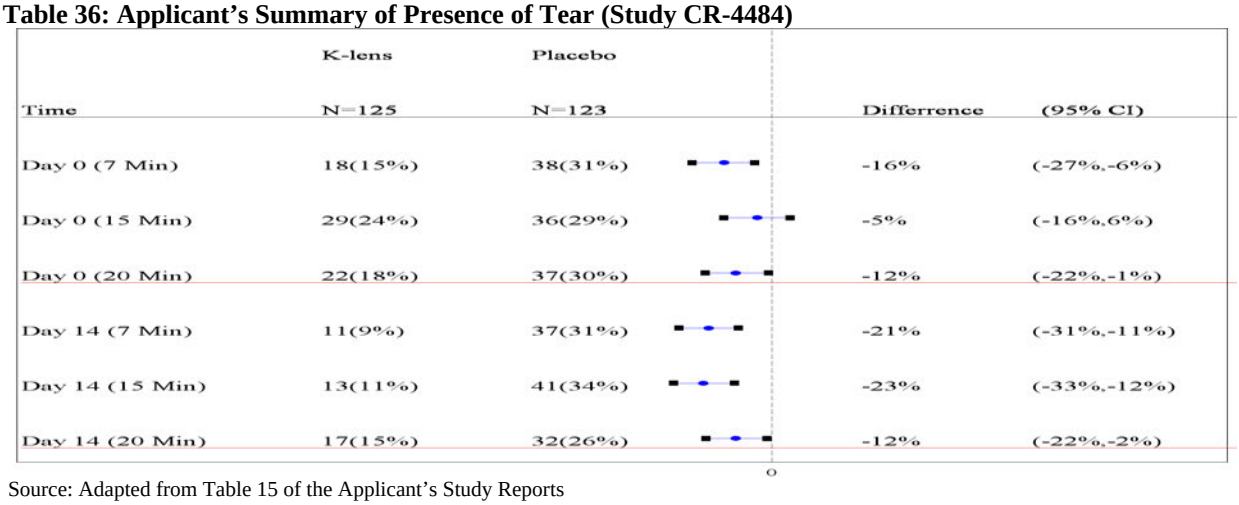
Table 35: Applicant's Summary of Presence of Tear (Study CR-4483)



Time	K-lens N=119	Placebo N=121	Difference	(95% CI)
Day 0 (7 Min)	9(8%)	22(18%)	-11%	(-19%,-2%)
Day 0 (15 Min)	10(9%)	16(13%)	-5%	(-13%,3%)
Day 0 (20 Min)	7(6%)	15(13%)	-7%	(-14%,1%)
Day 14 (7 Min)	5(4%)	13(12%)	-7%	(-14%,0%)
Day 14 (15 Min)	5(4%)	14(13%)	-8%	(-15%,-1%)
Day 14 (20 Min)	3(3%)	14(13%)	-10%	(-17%,-3%)

Source: Adapted from Table 15 of the Applicant's Study Reports

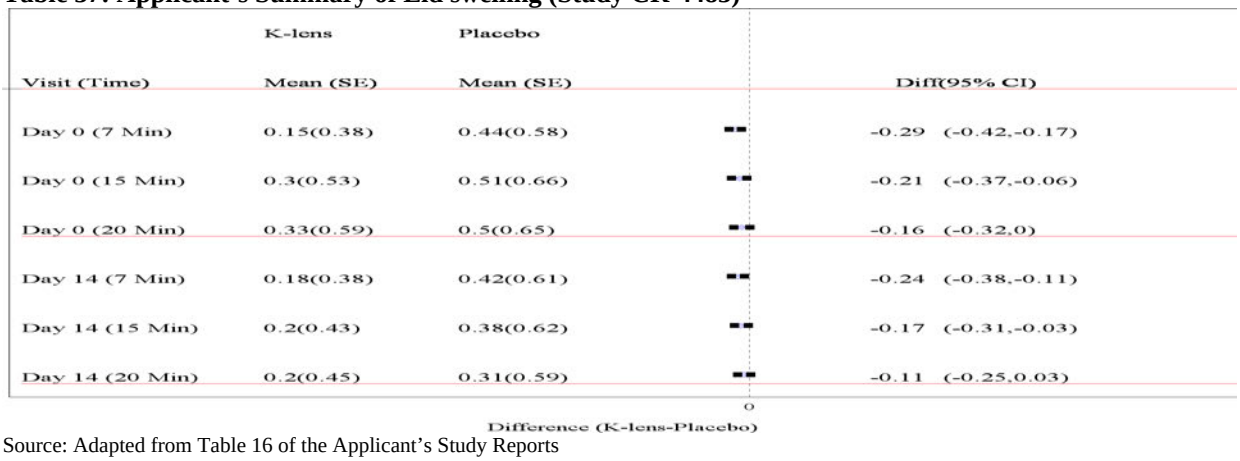
Table 36: Applicant's Summary of Presence of Tear (Study CR-4484)



Time	K-lens N=125	Placebo N=123	Difference	(95% CI)
Day 0 (7 Min)	18(15%)	38(31%)	-16%	(-27%,-6%)
Day 0 (15 Min)	29(24%)	36(29%)	-5%	(-16%,6%)
Day 0 (20 Min)	22(18%)	37(30%)	-12%	(-22%,-1%)
Day 14 (7 Min)	11(9%)	37(31%)	-21%	(-31%,-11%)
Day 14 (15 Min)	13(11%)	41(34%)	-23%	(-33%,-12%)
Day 14 (20 Min)	17(15%)	32(26%)	-12%	(-22%,-2%)

Source: Adapted from Table 15 of the Applicant's Study Reports

Table 37: Applicant's Summary of Lid swelling (Study CR-4483)



Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	0.15(0.38)	0.44(0.58)	-0.29 (-0.42,-0.17)
Day 0 (15 Min)	0.3(0.53)	0.51(0.66)	-0.21 (-0.37,-0.06)
Day 0 (20 Min)	0.33(0.59)	0.5(0.65)	-0.16 (-0.32,0)
Day 14 (7 Min)	0.18(0.38)	0.42(0.61)	-0.24 (-0.38,-0.11)
Day 14 (15 Min)	0.2(0.43)	0.38(0.62)	-0.17 (-0.31,-0.03)
Day 14 (20 Min)	0.2(0.45)	0.31(0.59)	-0.11 (-0.25,0.03)

Difference (K-lens-Placebo)

Source: Adapted from Table 16 of the Applicant's Study Reports

Table 38: Applicant's Summary of Lid swelling (Study CR-4484)

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 0 (7 Min)	0.26(0.52)	0.67(0.78)	-0.41 (-0.58,-0.25)
Day 0 (15 Min)	0.46(0.78)	0.82(0.89)	-0.36 (-0.57,-0.15)
Day 0 (20 Min)	0.52(0.85)	0.78(0.98)	-0.26 (-0.49,-0.03)
Day 14 (7 Min)	0.13(0.39)	0.5(0.66)	-0.37 (-0.5,-0.23)
Day 14 (15 Min)	0.17(0.44)	0.53(0.71)	-0.36 (-0.51,-0.21)
Day 14 (20 Min)	0.16(0.41)	0.5(0.75)	-0.35 (-0.5,-0.19)

Difference (K-lens-Placebo)

Source: Adapted from Table 16 of the Applicant's Study Reports

3.3 Evaluation of Safety

This section presents descriptive summaries of the percentages of treatment-emergent adverse events (TEAEs) using MedDRA 20.1 dictionary derived term, from Study CR-4483 and Study CR-4484. These summaries are provided for the safety analysis population, which is defined in the SAP as all randomized patients who receive study medication. Additional safety summary from two more studies conducted on healthy contact lens wearers is presented in the Appendix.

3.3.1 Adverse Events

Ocular adverse events (AEs) occurred in 9% of subjects (8% of eyes) in the K-Lens group compared to 3% of subjects (2% of eyes) in the placebo group. The Applicant reports that none of the ocular AEs were serious. The most common ocular AEs in the K-Lens group were eye pain, instillation site pain (each in 10 eyes [1.5%]) and eye irritation (11 eyes [1.7%]). Non-ocular AEs occurred in 22% of subjects in the K-Lens/K-Lens group and in 19% of subjects in the placebo/placebo group. The most common non-ocular AEs were nasopharyngitis (10 subjects [3.0%] in the K-Lens /K-Lens group and 2 subjects [1.2%] in the placebo/placebo group) and sinusitis (9 subjects [2.7%] in the K-Lens /K-Lens group and 1 subject [0.6%] in the placebo/placebo group).

Recall that K-Lens is a combination product which includes a contact lens and an anti-allergy medication. To evaluate the effect of adding the anti-allergy medication on visual acuity, the changes in contact lens corrected visual acuity from Visit 4 (pre-CAC with test article) to Visit 5 (pre-CAC with test article) were measured in terms of increases or decreases in the number of lines of Snellen visual acuity. The results in both studies showed that there was no significant difference in change in visual acuity between the K-Lens and placebo wearing eyes.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The analyses of the primary efficacy endpoint for selected subgroup of subjects are presented in Table 39-Table 50. The subgroup analyses provided results that were consistent with the Applicant's primary efficacy analysis results.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No major statistical issues were encountered in this review. However, there are two points that need to be considered when interpreting the findings of this review. These issues are related to the inadvertent disclosure of treatment assignments in one site in Study CR-4483 and failure by the study protocols to pre-specify the primary estimand.

- Per the Applicant, during a post-study assessment, it was discovered that the test article shipment sheet and study/site reconciliation worksheet inadvertently contained manufacturing lot information that identified the active (" K-Lens ") and placebo test articles and was shipped to Site 1 in Study CR-4483. Although the efficacy conclusions in the two sites are similar, breach of study blinding casts doubt on the integrity of the study.

- Neither the protocol nor the statistical analysis plan clearly specified the treatment difference (estimand) of interest. In the absence of a pre-specified estimand, a possible interpretation of the implied estimand taking the approaches used to deal with intercurrent events into considerations might be attempted. However, this approach should be discouraged as it opens the observed results to conflicting interpretations.

5.2 Collective Evidence

There was statistically significant reduction in mean itching score at each of the 6 timepoints in favor of K-Lens wearing eyes. However, compared to the placebo lens wearing eyes, a higher incidence of ocular and non-ocular adverse events was reported in the K-Lens wearing eyes. The most frequently reported ocular adverse events in the K-Lens wearing eyes were eye pain, instillation site pain and eye irritation. Ocular AEs that led to treatment discontinuation in the K-Lens group included conjunctivitis, corneal abrasion, dry eye, eye irritation and eye pruritus.

5.3 Conclusions

In conclusion, the results of the Applicant's and the reviewer's analyses of ocular itching presented in this review provide evidence to support the efficacy of K-Lens for the treatment of ocular itching due to allergic conjunctivitis. As noted, caution is advised when interpreting the findings of the secondary efficacy endpoints.

5.4 Labeling Recommendations

In the Clinical Section of the drug label, the Applicant provide the following summary:

In two double-masked, randomized, placebo-controlled [redacted] (b) (4) conjunctival allergen challenge (CAC) studies, ACUVUE® Theravision™ with Ketotifen was more effective than placebo

(1•DAY ACUVUE®) in preventing ocular itching in patients with allergic conjunctivitis induced by an ocular allergen challenge. ACUVUE® Theravision™ with Ketotifen reduced ocular itching within 3 minutes (b) (4) and the response was sustained for up to 12 hours after lens insertion.

Visual acuity was comparable between ACUVUE® Theravision™ with Ketotifen and 1•DAY ACUVUE®.

(b) (4)

Reviewer's Recommendation: The summary provided above is supported by the study results, and therefore, acceptable. However, the part which states that (b) (4) *should be moved to a* (b) (4) .

6 Appendix A: Selected Efficacy and Safety Summaries

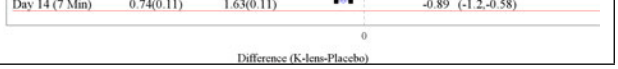
Table 39: Subgroup Analysis: Mean Ocular Itching (Sex: Female)

Study CR-4483

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.74(0.11)	1.93(0.11)	-1.19 (-1.49,-0.89)
Day 1 (5 Min)	0.88(0.1)	2.18(0.1)	-1.3 (-1.59,-1.01)
Day 1 (7 Min)	0.91(0.11)	2.02(0.11)	-1.11 (-1.41,-0.81)
Day 14 (3 Min)	0.38(0.1)	1.67(0.1)	-1.29 (-1.56,-1.02)
Day 14 (5 Min)	0.58(0.11)	1.89(0.11)	-1.32 (-1.62,-1.02)
Day 14 (7 Min)	0.54(0.11)	1.66(0.11)	-1.11 (-1.43,-0.8)

Study CR-4484

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.88(0.1)	1.87(0.1)	-0.99 (-1.28,-0.7)
Day 1 (5 Min)	0.99(0.11)	2.06(0.11)	-1.07 (-1.37,-0.77)
Day 1 (7 Min)	1.01(0.11)	2.01(0.11)	-1.01 (-1.31,-0.7)
Day 14 (3 Min)	0.49(0.1)	1.73(0.09)	-1.25 (-1.51,-0.98)
Day 14 (5 Min)	0.71(0.11)	1.82(0.1)	-1.12 (-1.41,-0.83)
Day 14 (7 Min)	0.74(0.11)	1.63(0.11)	-0.89 (-1.2,-0.58)



Source: Reviewer's Analysis.

Table 40: Subgroup Analysis: Mean Ocular Itching (Sex: Male)

Study CR-4483

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.46(0.1)	1.48(0.1)	-1.02 (-1.29,-0.75)
Day 1 (5 Min)	0.6(0.11)	1.74(0.1)	-1.14 (-1.44,-0.84)
Day 1 (7 Min)	0.67(0.12)	1.7(0.11)	-1.04 (-1.36,-0.71)
Day 14 (3 Min)	0.46(0.11)	1.54(0.11)	-1.07 (-1.38,-0.76)
Day 14 (5 Min)	0.55(0.11)	1.75(0.11)	-1.2 (-1.52,-0.88)
Day 14 (7 Min)	0.53(0.11)	1.72(0.11)	-1.19 (-1.5,-0.88)

Study CR-4484

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.57(0.12)	1.7(0.12)	-1.13 (-1.46,-0.8)
Day 1 (5 Min)	0.73(0.12)	2.01(0.12)	-1.28 (-1.63,-0.93)
Day 1 (7 Min)	0.65(0.12)	1.95(0.12)	-1.3 (-1.64,-0.96)
Day 14 (3 Min)	0.33(0.12)	1.7(0.11)	-1.37 (-1.69,-1.04)
Day 14 (5 Min)	0.34(0.1)	2.1(0.1)	-1.76 (-2.04,-1.47)
Day 14 (7 Min)	0.37(0.12)	2.12(0.11)	-1.75 (-2.08,-1.42)

Source: Reviewer's Analysis.

Table 41: Subgroup Analysis: Mean Ocular Itching (Age:18 years)

Study CR-4483

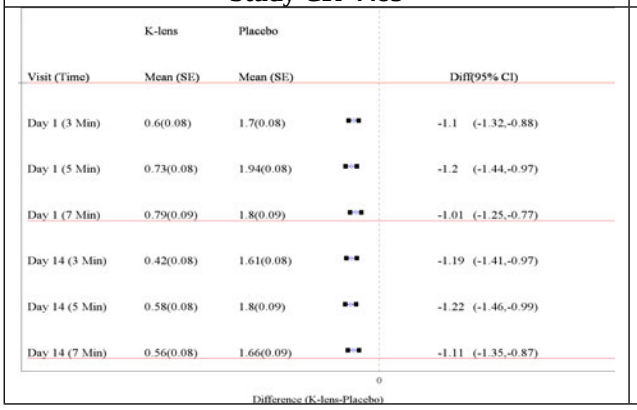
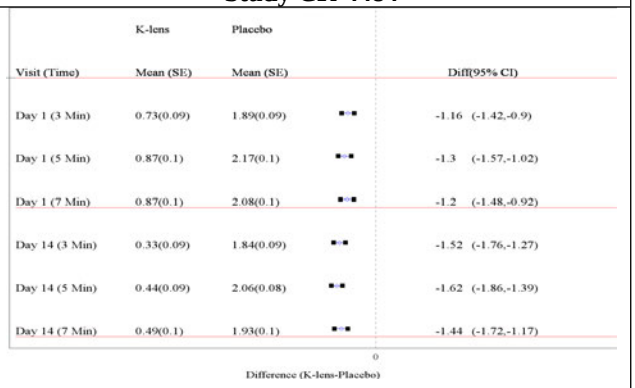
Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.88(0.31)	2.17(0.25)	-1.29 (-2.21,-0.38)
Day 1 (5 Min)	0.75(0.3)	2.42(0.25)	-1.67 (-2.57,-0.76)
Day 1 (7 Min)	0.63(0.43)	2.42(0.35)	-1.79 (-3.07,-0.51)
Day 14 (3 Min)	1(0.44)	1.67(0.36)	-0.67 (-1.99,0.66)
Day 14 (5 Min)	1.13(0.47)	1.75(0.38)	-0.63 (-2.02,0.77)
Day 14 (7 Min)	0.88(0.5)	1.42(0.41)	-0.54 (-2.02,0.94)

Study CR-4484

Visit (Time)	K-lens Mean (SE)	Placebo Mean (SE)	Diff(95% CI)
Day 1 (3 Min)	0.6(0.19)	1.48(0.19)	-0.88 (-1.41,-0.34)
Day 1 (5 Min)	0.68(0.19)	1.5(0.19)	-0.83 (-1.36,-0.29)
Day 1 (7 Min)	0.63(0.18)	1.6(0.18)	-0.98 (-1.49,-0.46)
Day 14 (3 Min)	0.45(0.19)	1.55(0.19)	-1.1 (-1.64,-0.56)
Day 14 (5 Min)	0.5(0.16)	1.88(0.16)	-1.38 (-1.82,-0.93)
Day 14 (7 Min)	0.43(0.17)	1.85(0.17)	-1.43 (-1.91,-0.94)

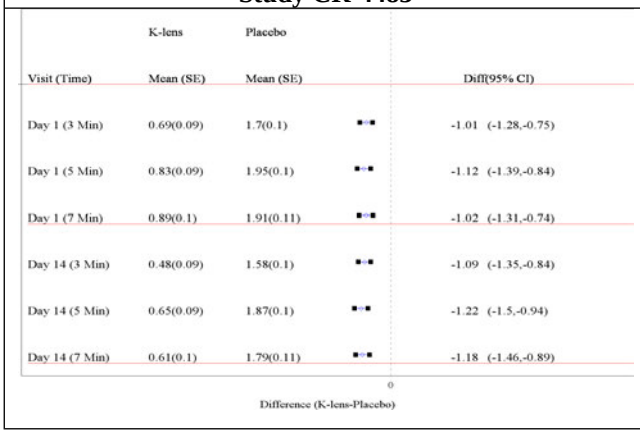
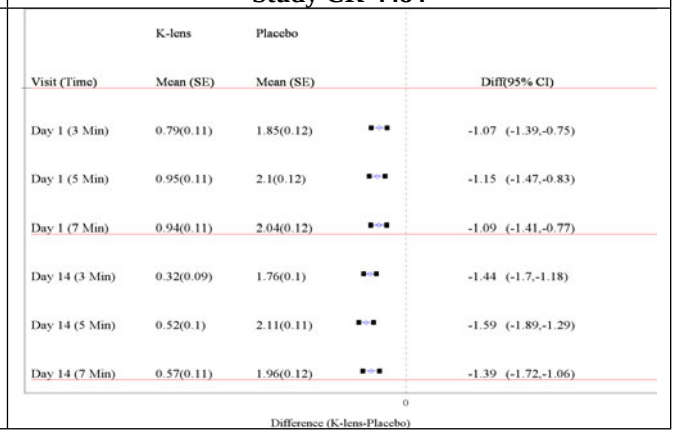
Source: Reviewer's Analysis.

Table 42: Subgroup Analysis: Mean Ocular Itching (Age: 18-40 years)

Study CR-4483	Study CR-4484
	

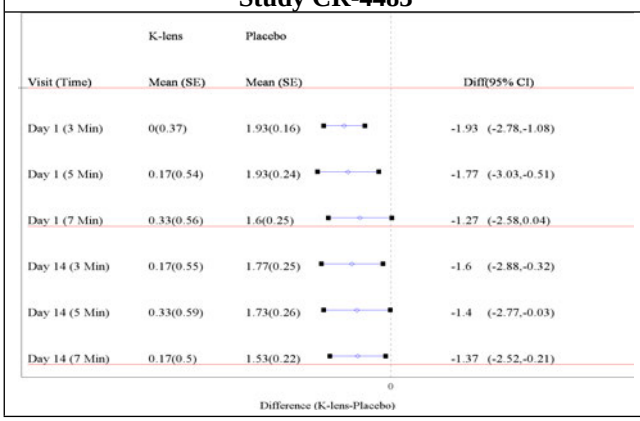
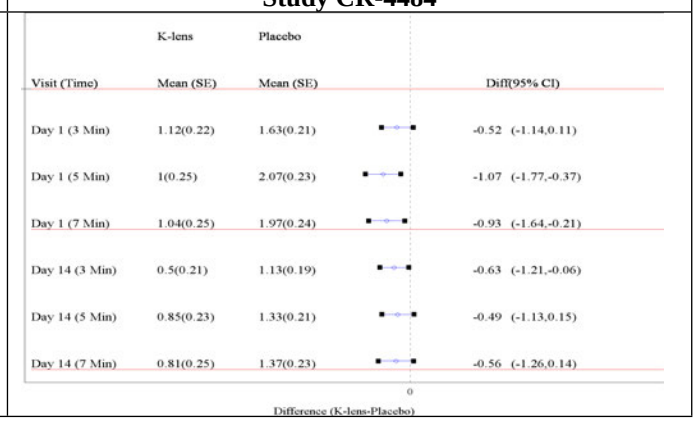
Source: Reviewer's Analysis.

Table 43: Subgroup Analysis: Mean Ocular Itching (Iris Color: Brown)

Study CR-4483	Study CR-4484
	

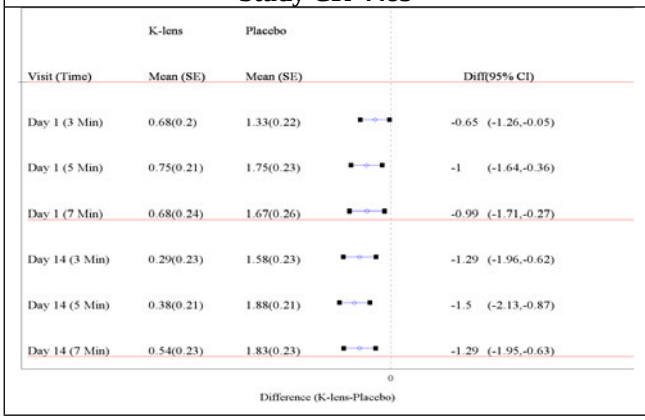
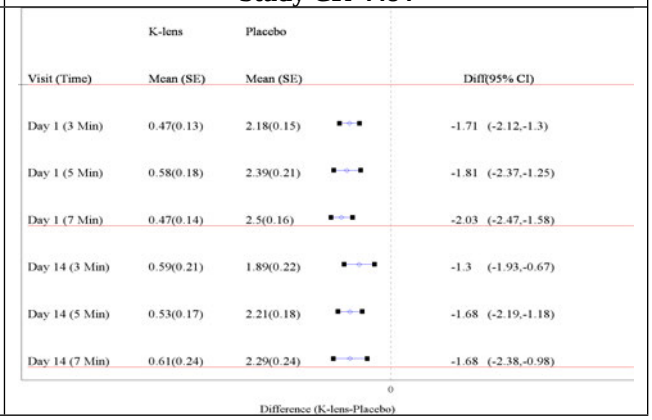
Source: Reviewer's Analysis.

Table 44: Subgroup Analysis: Mean Ocular Itching (Iris Color: Green)

Study CR-4483	Study CR-4484
	

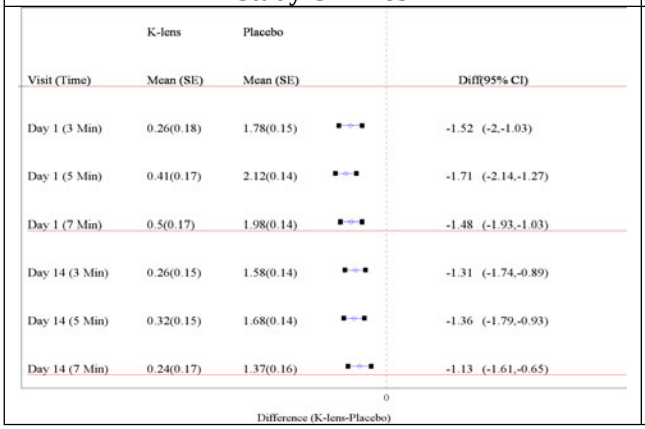
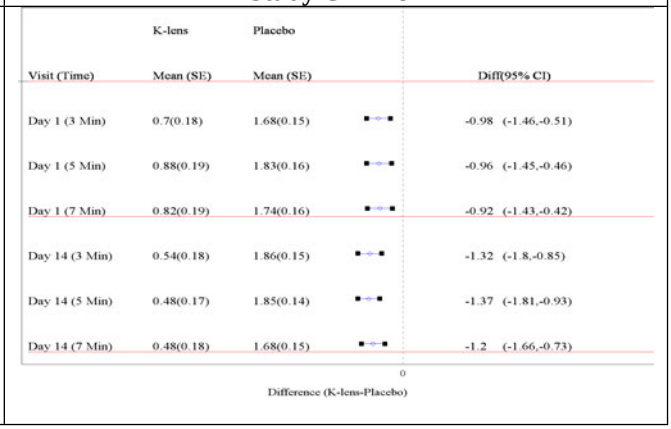
Source: Reviewer's Analysis.

Table 45: Subgroup Analysis: Mean Ocular Itching (Iris Color: Hazel)

Study CR-4483	Study CR-4484
	

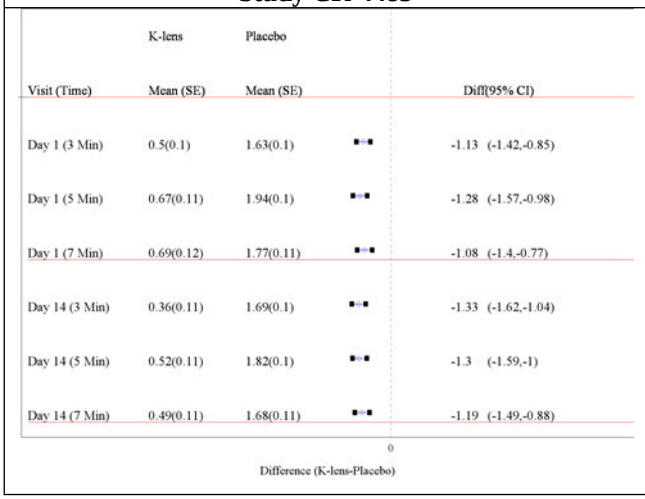
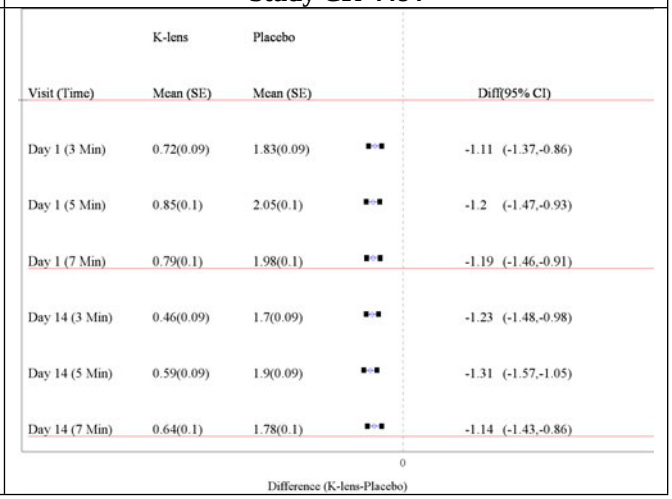
Source: Reviewer's Analysis.

Table 46: Subgroup Analysis: Mean Ocular Itching (Iris Color: Blue)

Study CR-4483	Study CR-4484
	

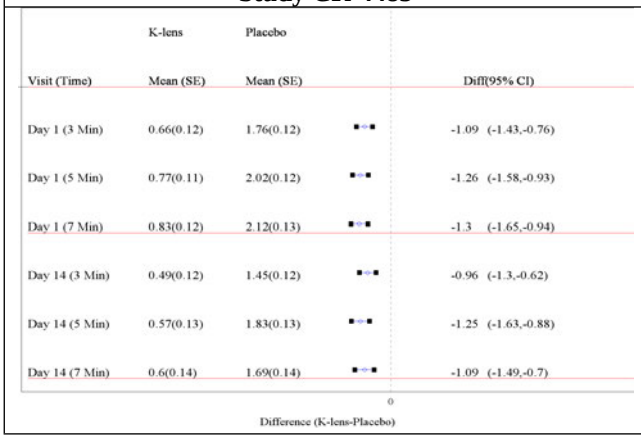
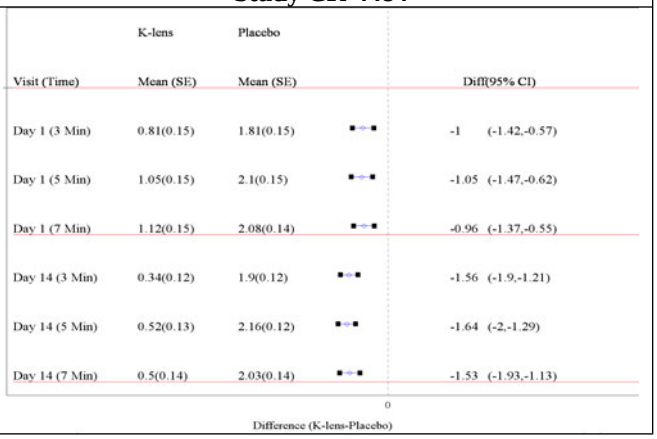
Source: Reviewer's Analysis.

Table 47: Subgroup Analysis: Mean Ocular Itching (Race: White)

Study CR-4483	Study CR-4484
	

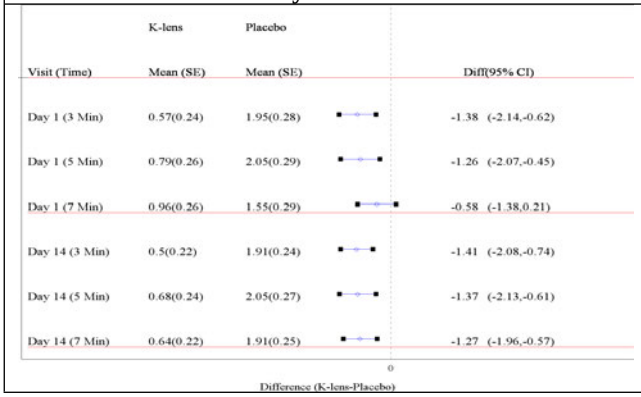
Source: Reviewer's Analysis.

Table 48: Subgroup Analysis: Mean Ocular Itching (Iris Color: Asian)

Study CR-4483	Study CR-4484
	

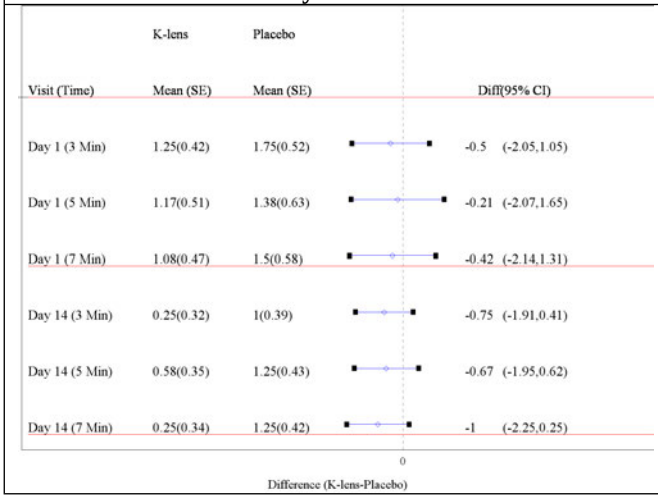
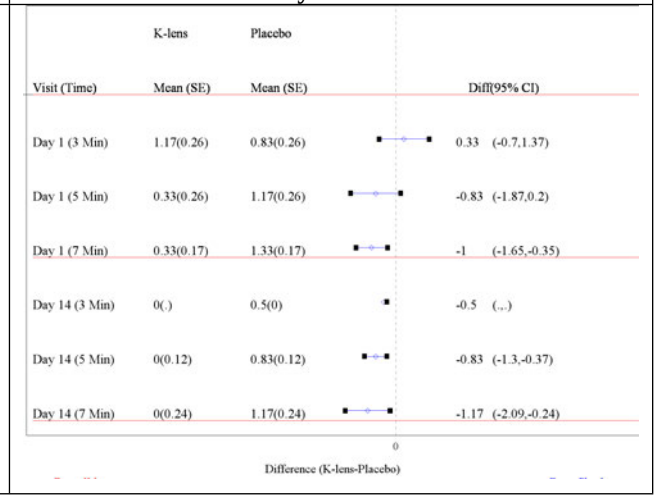
Source: Reviewer's Analysis.

Table 49: Subgroup Analysis: Mean Ocular Itching (Iris Color: Black or African American)

Study CR-4483	Study CR-4484
	This study has not enrolled any black or African American subjects

Source: Reviewer's Analysis.

Table 50: Subgroup Analysis: Mean Ocular Itching (Iris Color: Others)

Study CR-4483	Study CR-4484
	

Source: Reviewer's Analysis.

7 Appendix A: Summary of Other Completed Studies

In addition to the two pivotal studies used for the evaluation of safety and efficacy of K-Lens, the Applicant conducted two Phase 3 studies, CR-4490 and CR-4539. Both these studies were conducted in healthy contact lens wearers to evaluate the long-term safety of K-Lens. This section presents the summary of these two studies.

7.1 Study CR CR-4490

This was a multi-center, randomized, double-masked, placebo controlled, parallel-group study. The objective of this study was to evaluate the safety and tolerability of daily K-Lens wear in healthy, contact lens wearers over a 12-week period.

Demographic and Baseline Characteristics

The study enrolled a total of 241 subjects including 30 pediatric subjects, who ranged in age from 11 to 17. The 241 eligible subjects were randomized to K-Lens (n=160) or Placebo (n=81). There were no significant imbalances between the two arms in the demographics of age, gender, and race (Table 51). Subjects were predominantly Caucasian (83.8%) and of non-Hispanic ethnicity (99.2%). Overall, more females than males (74.3% vs. 25.7%, respectively) were randomized in the study; the gender ratio was similar within each treatment group; with each treatment group at least 73% female and at least 24% male. Most subjects in both arms had brown iris color.

Table 51: Baseline and Demographic Characteristics (Study CR-4490)

	Treatment Groups		
	K-Lens N=160	**Placebo N=81**	**Overall N=241**
Age (mean years ±SD) Median (Minimum, Maximum)	31.1±12 28 (11,61)	31.0±10.8 28 (13, 54)	31.1±11.6 28 (11, 61)
Sex n (%)			
Female	117 (73.1)	62 (76.5)	179 (74.3)
Male	43 (26.9)	19 (23.5)	62 (25.7)
Race n (%)			
Caucasian	131 (81.9)	71 (87.7)	202 (83.8)
Asian	3 (1.9)	1 (1.2)	4 (1.7)
African American	24 (15.0)	8 (9.9)	32 (13.3)
Other	2 (1.3)	1 (1.2)	3 (1.2)

Source: Table 4 of the Applicant's Study Reports.

Table 52: Iris Color (Per Eye) Study CR-4490)

	Treatment Groups		
	K-Lens N=320	**Placebo N=162**	**Overall N=482**
Iris Color n (%)			
Brown	132 (42.5)	64 (39.5)	200 (41.5)
Blue	96 (30.0)	50 (30.9)	146 (30.3)

Hazel	48 (15.0)	22 (13.6)	70 (14.5)
Green	40 (12.5)	26 (16.1)	66 (13.7)

Source: Table 5 of the Applicant's Study Reports.

Subject Disposition

Of the 160 subjects randomized to treatment with K-Lens, 150 (93.8%) completed the study, and of the 81 subjects randomized to placebo treatment, 78 completed the study (96.3%). None of the pediatric subjects was prematurely discontinued from the study. The main reasons for treatment discontinuation in the K-Lens group are listed as subject choice and adverse events.

Table 53: Subject Disposition (Study CR-4490)

	Treatment Groups		
Population, n (%)	**K-Lens N=160**	**Placebo N=81**	**Overall N=241**
Safety population	160 (100)	81 (100)	241 (100)
Completed the study	150 (93.8)	78 (96.3)	228 (94.6)
Discontinued the study	10 (6.2)	3 (3.7)	13 (5.4)
Reason for Discontinuation			
Subject Choice	4 (2.5)	0 (0.0)	4 (1.7)
Adverse Event	3 (1.9)	0 (0.0)	3 (1.2)
Other	2 (1.3)[1]	3 (3.7)[2]	5 (2.1)
Lost to follow-up	1 (0.6)	0 (0.0)	1 (0.4)
Modified Per protocol population	137 (85.6)	68 (84)	205 (85.1)

Source Table 3 of the Applicant's Study Reports. [1] Subject (b) (6) was discontinued because she was enrolled in another investigational device trial. [2] Subject (b) (6) was unable to complete the study because of scheduled LASIK surgery. [2]Subjects (b) (6) and (b) (6) were discontinued because they received disallowed medications.

Adverse Events

Per the study results, ocular treatment-emergent AEs were reported in 5.0% (8/160) and 1.2% (1/81) of subjects in the K-Lens and placebo lens treatment groups, respectively. Non-ocular treatment-emergent AEs were reported in 29.4% (47/160) and 24.7% (20/81) of subjects in the K-Lens and placebo lens treatment groups, respectively. The Applicant also reports that, treatment-emergent test article-related AEs were reported in 3.1% (5/160) and 1.2% (1/81) of subjects in the K-Lens and placebo lens treatment groups, respectively. Two subjects (K-Lens) experienced 2 serious non-ocular adverse events. No subjects died over the course of this study.

7.2 Study CR CR-4539

This was a single-center, randomized, double-masked, placebo-controlled, parallel-group study. The objective of this study was to evaluate the safety of K-Lens for up to 12 weeks.

Demographic and Baseline Characteristics

The safety population (randomized and treated) is comprised of 250 subjects including 33 pediatric subjects, who ranged in age from 11 to 17. The 250 eligible subjects were randomized to K-Lens (n=168) or Placebo (n=82). Subjects were predominantly Caucasian (76.0%) and of non-Hispanic ethnicity (98.4%). Overall, more females (65.2%) than males (34.8%) were

randomized to treatment in the study. The majority of subjects had brown eyes (232 eyes;46.4%), followed by blue (122 eyes, 24.4%), hazel (82 eyes; 16.4%), and green (64 eyes;12.8%; Table 54 and Table 55).

Table 54: Baseline and Demographic Characteristics (Study CR-4539)

	Treatment Groups		
	K-Lens N=168	**Placebo N=82**	**Overall N=250**
Age (mean years ±SD) Median (Minimum, Maximum)	32.6±12.5 31 (11,62)	29.3±10.8 27 (13, 66)	31.5±12.3 30 (11, 66)
Sex n (%)			
Female	117 (69.4)	46 (56.1)	163 (65.2)
Male	51 (30.4)	36 (43.)	87 (34.8)
Race n (%)			
Caucasian	129 (76.8)	61 (74.4)	190 (76.0)
Asian	3 (1.8)	1 (1.2)	4 (1.6)
African American	36 (21.4)	18 (21.9)	54 (21.6)
Other	0 (0.0)	2 (2.4)	2 (0.8)

Source: Table 5 of the Applicant's Study Reports.

Table 55: Iris Color (Per Eye) Study CR-4539)

	Treatment Groups		
	K-Lens N=336	**Placebo N=164**	**Overall N=500**
Iris Color n (%)			
Brown	154 (45.8)	78 (47.5)	232 (46.4)
Blue	80 (23.8)	42 (25.6)	122 (24.4)
Hazel	52 (15.4)	30 (18.3)	82 (16.4)
Green	50 (14.9)	14 (8.5)	64 (12.8)

Source: Table 5 of the Applicant's Study Reports.

Subject Disposition

Of the 168 subjects randomized to treatment with K-Lens, 161 (95.8%) completed the study, and of the 82 subjects randomized to placebo treatment, 78 (95.1%) completed the study. In the placebo lens group, 4 subjects (4.9%) were discontinued from the study due to 4 AEs (2 non-ocular and 2 ocular both of which were conjunctivitis). In the K-Lens group, 2 subjects (1.2%) were discontinued from the study due to AEs, 3 subjects (1.8%) due to withdrawn consent (subject choice), and 2 subjects (1.2%) for reasons classified as "other."

Table 56: Subject Disposition (Study CR-4539)

	Treatment Groups		
Population, n (%)	**K-Lens N=168**	**Placebo N=82**	**Overall N=250**
Safety population	168 (100)	82 (100)	250 (100)
Completed the study Blue	161 (95.8)	78 (91.5)	239 (95.6)
Discontinued the study	7 (4.1)	4 (4.9)	11 (4.4)
Reason for Discontinuation			
Subject Choice	3 (1.8)	0 (0.0)	3 (1.2)

Adverse Event	2 (1.2)	4 (4.9)	6 (2.4)
Other	2 (1.2)	0 (0.0)	2 (0.8)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Per protocol population	158 (94.0)	75 (95.1)	233 (93.2)

Source Table 3 of the Applicant's Study Reports.

Adverse Events

Per the study results, ocular treatment-emergent AEs were reported in 13.1% (22/168) and 4.9% (4/82) of subjects in the K-Lens and placebo lens treatment groups, respectively. Non-ocular treatment-emergent AEs were reported in 14.3% (24/168) and 13.4% (11/82) of subjects in the K-Lens and placebo lens treatment groups, respectively. Treatment-emergent test article-related AEs were reported in 8.9% (15/168) and 0% (0/82) of subjects in the K-Lens and placebo lens treatment groups, respectively. No subject died over the course of this study. One subject (K-Lens) experienced 2 serious non-ocular adverse events.

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