CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22388
Priority or Standard	Standard
Submit Date(s)	4/30/2021
Received Date(s)	4/30/2021
PDUFA Goal Date	2/28/2022
Division/Office	DO/OSM
Reviewer Name(s)	Rhea A. Lloyd, MD
Review Completion Date	See DARRTS Stamp Date
Established/Proper Name	etafilcon A drug-eluting contact lens with ketotifen
(Proposed) Trade Name	ACUVUE Theravision with Ketotifen
Applicant	Johnson and Johnson Vision Care, Inc.
Dosage Form(s)	ophthalmic device and topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	• Insert one lens per eye per day. • No more than one ACUVUE® Theravision™ with Ketotifen per eye per day should be used. • If prevention or relief from itching is needed beyond twelve hours, remove ACUVUE® Theravision™ with Ketotifen and consult your eye care professional. • ACUVUE® Theravision™ with Ketotifen may be worn beyond twelve hours for vision correction. Lenses should be removed prior to sleeping.
Recommended Indication(s)/Population(s)	Indicated for the prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1.00 D of astigmatism
Recommendation on Regulatory Action	Approval

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

K-Lens is a combination product that contains ketotifen fumarate, an antihistamine, and a daily disposable etafilcon A contact lens. Several different K-Lens formulations were tested during the clinical development program. The nominal dose of 0.019 mg ketotifen/lens (represented as K-Lens 25) was included in all 13 clinical studies, which is the proposed commercial dose.

Ketotifen fumarate is the active ingredient in several currently marketed over-the-counter (OTC) ophthalmic medications indicated for the prevention of ocular itching associated with allergic conjunctivitis. It is a relatively selective H1 antihistamine/mast cell stabilizer.

The etafilcon A (FDA Group IV), soft hydrophilic contact lens is a daily disposable contact lens. Etafilcon A is a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid cross linked with 1,1,1-trimethylol propane trimethacrylate and ethylene glycol dimethacrylate. The lenses are tinted with (b) (4) to improve visibility and handling. (b) (4) .

1.2. Conclusions on the Substantial Evidence of Effectiveness

From a clinical perspective, NDA 22388 is recommended for approval with the labeling revisions found in this review. The application supports the safety and effectiveness of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for prevention ocular itch due to allergic in patients who do not have red eye(s) and are suitable for contact lens wear.

1.3. Benefit-Risk Assessment

Benefit-Risk Dimensions

Benefit-Risk Integrated Assessment

The adequate and well controlled studies contained in this submission establish the efficacy of ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen), nominal dose of 0.019 mg ketotifen/lens, for prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1.00 D of astigmatism.

Studies CR-4483 and CR-4484 demonstrated superiority of ACUVUE Theravision with Ketotifen compared to ACUVUE daily contact lens (without ketotifen) for the intended indication. The most common ocular adverse events after treatment with ACUVUE Theravision with Ketotifen observed in the submitted clinical studies were eye irritation, eye pain, instillation site irritation, dry eye, photophobia and mydriasis.

There is a favorable benefit-risk ratio of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for the prevention of ocular itch due to allergic conjunctivitis who do not have red eye(s) and correction of refractive ametropia (myopia and hyperopia) in patients who are suitable for contact lens wear or more than 1.00 D of astigmatism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ocular allergies affect more than 20% of the general population.	The goal of treatment of ACUVUE Theravision with Ketotifen is to prevent ocular itching in patients who have refractive ametropia and are contact lens wearers.
Current Treatment Options	• There are no combination antihistamine and contact lens therapies approved. • Many topical ophthalmic antihistamines are approved for the treatment of ocular allergies. These therapies require contact lens wearers to wait at least 10 minutes after instillation before lens insertion to prevent absorption of benzalkonium chloride by soft contact lenses.	ACUVUE Theravision with Ketotifen was superior to ACUVUE daily contact lens alone in the prevention of ocular itch due to allergic conjunctivitis. This product, if approved, would provide a new therapeutic option for contact lens wearers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Studies CR-4483 and CR-4484 demonstrated that ACUVUE Theravision with Ketotifen was superior to ACUVUE daily wear contact lens without ketotifen (placebo lens) in the prevention of ocular itch due to allergic conjunctivitis in conjunctival allergen challenge studies with an onset of action as soon as 3 minutes post-CAC and a duration of action of up to 12 hours of lens wear. • When used as clinically indicated, K-Lens is safe for use in patients with refractive ametropia (myopia and hyperopia) and allergic conjunctivitis. No clinically significant or unexpected ocular or non-ocular AEs were identified in clinical studies. The use of K-Lens did not appear to negatively affect visual acuity.	Adequate and well controlled studies support the efficacy the prevention of ocular itch due to allergic conjunctivitis in contact lens wearers.
Risk and Risk Management	• Ocular allergies can cause ocular hyperemia. K-Lens is intended to be used prior to the onset of the ocular allergic symptoms. As such, (b) (4) specifies that K-Lens is to be used in patients without ocular hyperemia. • The proposed product labeling contains a contraindication and a warning against wearing lenses if eye(s) are red and instructs patients to remove lenses immediately if eye(s) become red while wearing the lenses. • ACUVUE Theravision with Ketotifen in studies CR-4483, CR-4484, CR-4490, and CR-4590 demonstrated an acceptable safety profile.	Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

1.4. Patient Experience Data

Regarding clinical trials CR-4483, CR-4484, CR-4490, and CR-4539

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:						Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as					Sec 6. Study endpoints
		x	Patient reported outcome (PRO)				
		□	Observer reported outcome (ObsRO)				
		x	Clinician reported outcome (ClinRO)				
		□	Performance outcome (PerfO)				
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)					
	□	Patient-focused drug development or other stakeholder meeting summary reports					
	□	Observational survey studies designed to capture patient experience data					
	□	Natural history studies					
	□	Patient preference studies (e.g., submitted studies or scientific publications)					
	□	Other: (Please specify)					
□	Patient experience data that were not submitted in the application, but were considered in this review:						
		□	Input informed from participation in meetings with patient stakeholders				
		□	Patient-focused drug development or other stakeholder meeting summary reports				
		□	Observational survey studies designed to capture patient experience data				
		□	Other: (Please specify)				
□	Patient experience data was not submitted as part of this application.						

2. Therapeutic Context

2.1. Analysis of Condition

Ocular allergies affect > 20% of the general population. These disorders are immunoglobulin E (IgE)-dependent (Type 1) hypersensitivity inflammatory responses and primarily include seasonal allergic conjunctivitis and perennial allergic conjunctivitis. In susceptible individuals, ocular exposure to an allergen triggers an inflammatory cascade that is spurred primarily by histamine release and culminates in the characteristic signs and symptoms of ocular allergy disorders: itching, redness, swelling of the eyelid, chemosis, and tearing.

2.2. Analysis of Current Treatment Options

There is no currently approved combination treatment for both refractive ametropia and ocular itching associated with allergic conjunctivitis.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) is not approved in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 3.2: Summary of K-Lens US FDA Interactions

Interaction Type	Primary Purpose of Interaction	Date
Pre-IND Meeting	Clinical, CMC	24 November 2003
RFD Acceptance	Request for Designation	15 July 2004
End of Phase 2 Meeting	Clinical, CMC	1 December 2006
Type B Meeting	Clinical	25 June 2008
Type B Meeting	CMC	3 October 2008
Type C Meeting	Clinical, Parametric Release	20 October 2009 (WRO)
Type C Meeting	Clinical	26 April 2011
Type C Meeting	CMC, Non-Clinical	9 May 2014
Type C Meeting	CMC	5 November 2015
Type C Meeting	Clinical, CMC	13 June 2017
Type C Meeting	Labeling, Advisory Committee	8 17 February 2021
Type B Meeting	Pre-NDA	23 March 2021 (WRO)

Abbreviations: CMC=chemistry, manufacturing, and controls; IND=investigational new drug; NDA=new drug application; RFD=request for designation; WRO=written responses only

3.3. Foreign Regulatory Actions and Marketing History

ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) was launched in Canada, on May 10, 2021, and in Japan, on June 25, 2021.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI Clinical Inspections were not performed for this application.

4.2. Product Quality

The combination product, referred to as K-Lens, consists of the combination of a device (etafilcon A soft hydrophilic contact lens) with a drug (0.019 mg of ketotifen). See the Office of Product Quality review for additional details.

Composition (b) (4)

Component	Function	(% w/w)
2-Hydroxyethyl Methacrylate (HEMA)	(b) (4)	
Methacrylic acid (MAA)		
Ethylene Glycol Dimethacrylate (EGDMA)		
1,1,1-Trimethylolpropane Trimethacrylate (TMPTMA)		
(b) (4)		
Blue 2-Hydroxyethyl Methacrylate (Blue HEMA)	Visibility Tint	(b) (4)
(b) (4)		
(b) (4)		

Composition of Buffered Ketotifen Solution (BKS)

Component	Function	(% w/w)
Ketotifen Fumarate	Active	0.0043
Pentetic Acid[a]	(b) (4)	
Calcium Hydroxide[a]		
Sodium Chloride		
(b) (4)		
Boric Acid		
Purified Water		
(b) (4)		

Composition of K-Lens

Component	Function	Quantity
etafilcon A Contact Lens	Device Component	1 Device
Buffered Ketotifen Solution	Drug Component	(b) (4)

(b) (4)

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

There are no adequate and well-controlled studies of ACUVUE Theravison with Ketotifen administration in pregnant women to inform a drug-associated risk. ACUVUE Theravison with Ketotifen is not absorbed systemically following ocular administration, and maternal use is not expected to result in fetal exposure to the drug. Oral administration of ketotifen fumarate to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

No information is available on the carcinogenic potential of ketotifen fumarate.

See the Pharmacology/Toxicology review for additional details.

4.5. Clinical Pharmacology

Device Component

In its hydrated state, the lens when placed on the cornea, acts as a refracting medium to focus light rays on the retina to correct refractive ametropia for as long as the lens is worn (up to 24 hours while awake). (b) (4)

Drug Component

Ketotifen fumarate, a benzocycloheptathiophene derivative, is a H1 receptor antagonist that stabilizes mast cells and prevents eosinophil accumulation. This action prevents the onset of ocular allergic itch allowing for continued lens wear during episodes of allergen exposure. See the Clinical Pharmacology review for additional details.

4.6. Devices and Companion Diagnostic Issues

See the CDRH review dated August 16, 2021, for details.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
Controlled Studies to Support – Safety and Efficacy[1]					
CR-4483 Phase 3 Module 5.3.5.1	Study Design: Randomized, double-masked, placebo-controlled, multi-center study Evaluations: Safety and efficacy of K-Lens compared to a placebo lens for the prevention of ocular itching associated with allergic conjunctivitis induced by the CAC	120	Group 1: K-Lens in 1 eye and placebo lens in the other eye (n=41) K-Lens in left eye and placebo lens in right eye (n~20) K-Lens in right eye and placebo lens in left eye (n~20) Group 2: K-Lens in both eyes (n=39) Group 3: placebo lens both eyes (n=40)	Visit 1: Allergen titration, contact lens fitting Visit 2: Allergen challenge with CLs in place Visit 3: Confirm dose, re-challenge Visit 4: Subjects randomized; allergen challenged 12 hours post lens insertion Visit 5: Repeat of V4 randomized treatment, allergen challenged 15 min post lens insertion.	Primary Efficacy Measure at 3-, 5-, and 7-minutes post CAC at Visits 4 and 5: • Ocular itching scores were evaluated by the subject using a 0-4 scale. Secondary Efficacy Measures at 7-, 15-, and 20-minutes post CAC at Visits 4 and 5: • Ciliary hyperemia, conjunctival hyperemia, and episcleral hyperemia were evaluated by the investigator (0-4 scale) • Chemosis evaluated by the investigator (0-4 scale) • Mucous discharge evaluated by the investigator (absent or present) • Tearing evaluated by the investigator as absent or present. • Lid swelling evaluated by the subject (0-3 scale)

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
CR-4484 Phase 3 Module 5.3.5.1	Study Design: Randomized, double-masked, placebo-controlled, multi-center study Evaluations: Safety and efficacy of K-Lens compared to a placebo lens for the prevention of ocular itching associated with allergic conjunctivitis induced by the CAC	124	Group 1: K-Lens in 1 eye and placebo lens in the other eye (n=41) K-Lens in left eye and placebo lens in right eye (n~20) K-Lens in right eye and placebo lens in left eye (n~20) Group 2: K-Lens in both eyes (n=41) Group 3: placebo lens both eyes (n=42)	Visit 1: Allergen titration, CL fitting Visit 2: Allergen challenge (CLs in place) Visit 3: Confirm dose, re-challenge Visit 4: Randomization; allergen challenge 12 hrs post lens insertion Visit 5: Repeat of V4 randomized treatment, allergen challenge 15 min post lens insertion.	Primary Efficacy Measure at 3-, 5-, and 7-minutes post CAC at Visits 4 and 5: • Ocular itching scores were evaluated by the subject using a 0-4 scale. Secondary Efficacy Measures at 7-, 15-, and 20-minutes post CAC at Visits 4 and 5: • Ciliary hyperemia, conjunctival hyperemia, and episcleral hyperemia (0-4 scale) • Chemosis (0-4 scale) • Mucous discharge (absent or present) • Tearing (absent or present) • Lid swelling (0-3 scale)

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
Safety and Tolerability Studies – Phase 3					
CR-4490 Phase 3 Module 5.3.5.1	Study Design: Randomized, double-masked, placebo-controlled, parallel-group, multicenter study Evaluations: Safety and tolerability of K-Lens, an antihistamine-releasing CLs, in healthy CL wearers	241	K-Lens (bilateral) [Formulation 13 and 15] N=206 Placebo Lens (bilateral) N=106	Randomized (2:1) subjects were fit with CLs which were worn ≥8 hours/day, ≥5 days per week over 12 wks. CLs usage was recorded in study diary. 6 follow-up exams were scheduled over 12 weeks.	The following measurements were used to evaluate safety: • adverse events • slit lamp biomicroscopy (incl. corneal fluorescein staining) • visual acuity (best corrected and contact-lens corrected) • IOP (if possible, age ≥ 10 years old) • ophthalmoscopy (dilated) • physical exam (incl. vital signs) • pupil reactivity measurement
CR-4539 Phase 3 Module 5.3.5.1	Study Design: Randomized, double-masked, placebo-controlled, parallel-group, single center study Evaluations: Safety and tolerability of K-Lens, an antihistamine-releasing CLs, in healthy CL wearers	250	K-Lens (bilateral) [Formulation 7, 8, 13] N=168 Placebo Lens (bilateral) N=82	Randomized (2:1) subjects were fit with CLs which were worn ≥8 hours/day, ≥5 days per week over 12 wks. CLs usage was recorded in study diary. 6 follow-up exams were scheduled over 12 weeks.	The following measurements were used to evaluate safety: • adverse events • slit lamp biomicroscopy (incl. corneal fluorescein staining) • visual acuity (best corrected and contact-lens corrected) • IOP (if possible, age ≥ 10 years old) • ophthalmoscopy (dilated) • physical exam (incl. vital signs) • pupil reactivity measurement

1 The 2 Phase 3 efficacy studies (Study CR-4483 [Mod5.3.5.1] and Study CR-4484 [Mod5.3.5.1]) were identical in design.

5.2. Review Strategy

Clinical data for Studies CR-4483 and CR-4484 listed in Section 5.1 were reviewed to support safety and efficacy. Clinical data from Studies CR-4483, CR-4484, CR-4490 and CR-4539 were reviewed to support safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Studies CR-4483: A Multi-Center, Randomized, Double-Masked, Placebo-Controlled Evaluation of the Efficacy and Safety of K-Lens as Compared to Placebo Lens in the Prevention of Allergic Conjunctivitis in a Population of Allergic Contact Lens Wearers in the Conjunctival Allergen Challenge (CAC) Model

Reviewer's Comment:
The Phase 3 clinical development plan included two studies, CR-4483 and CR-4484, which are identical in design and were conducted in parallel. There were no differences in study objectives, protocol design, population studied, inclusion and exclusion criteria, planned treatment groups, treatment schedules, study assessments, efficacy endpoints, or statistical analysis methods.

6.1.1. Study Design

Overview and Objective

To evaluate the efficacy and safety of K-Lens compared to a placebo lens in contact lens wearing subjects for the prevention of ocular itching associated with allergic conjunctivitis induced by the CAC.

Study Investigators

Study CR-4483

Site Number	Principal Investigator Site Address	Number of Subjects Randomized
1	Eugene McLaurin, MD, Total Eye Care, 6060 Primacy Parkway, Ste 200, Memphis, Tennessee 38119	68
2	Fred Kurata, MD, East West Eye Institute, 1300 W 155th Street #104, Gardena, California 90247	42

Study CR-4484

Site Number	Principal Investigator Site Address	Number of Subjects Randomized
1	Robert L. Jones, MD, FACS; 1401 Avocado Avenue, Suite 505; Newport Beach, CA 92660	17
2	Gail Torkildsen, MD; Ophthalmic Research Associates, 863 Turnpike Street, North Andover, MA 01845	44
3	Edward J. Meier, MD; Eye Care Associates of Greater Cincinnati, Inc.; 5378 D. Cox Smith Road, Mason, OH 45040	23
4	Thomas J. Macejko, MD; Eye Care Associates of Greater Cincinnati, Inc.; 5378 D. Cox Smith Road, Mason, OH 45040	13
5	Mark T. Bergmann, MD; Eye Care Associates of Greater Cincinnati, Inc.; 5378 D. Cox Smith Road, Mason, OH 45040	23
6	Jung Dao, MD; Cornea Consultants of AZ, 3811 E. Bell Road, #306, Phoenix, AZ 85032	0

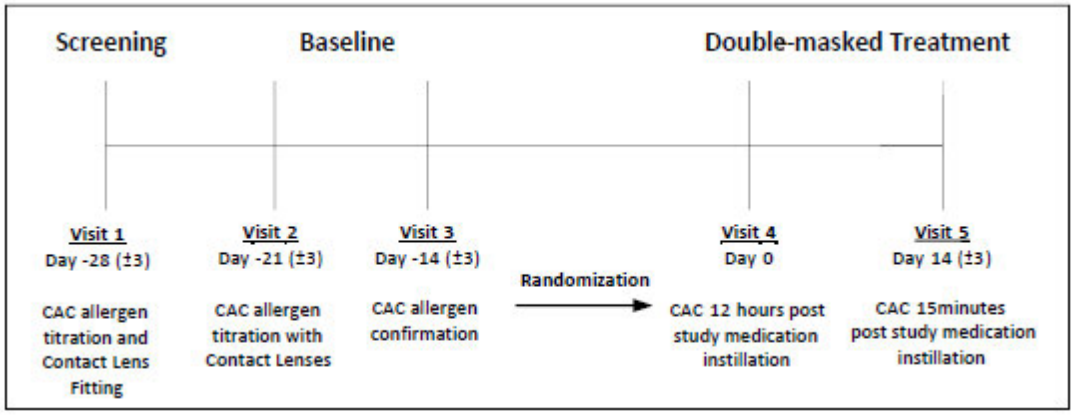
Trial Design

These identical studies were Phase 3, randomized by eye, double-masked, placebo-controlled conjunctival antigen challenge (CAC) in design. The study design included treatment groups wearing K-Lens and placebo lens in each eye and consisted of 5 visits over approximately a 6-week period.

- At Visit 1, subjects were screened, and if they met the inclusion/exclusion criteria, signed an informed consent form or assent form for subjects aged less than 18 years. First, allergen was titrated to achieve a positive ocular allergic reaction, then *1•DAY* ACUVUE® Brand Contact Lenses (*1•DAY* ACUVUE®) were fitted.
- At Visit 2, while wearing *1•DAY* ACUVUE®, subjects were challenged with allergen (beginning with 1 dose lower than the final dose that achieved a qualifying reaction at Visit 1). If a subject failed to react positively to the allergen, the subject was re-challenged with a higher dose to achieve a qualifying reaction on graded scales of ≥ 2.0 hyperemia in 2 of 3 vessel beds and ≥ 2.0 itching within 10 minutes of allergen instillation.
- At Visit 3, to confirm the allergen dose, subjects were challenged with the dose of allergen that they reacted to positively at Visit 2.
- At Visit 4, subjects were randomized into 1 of 3 treatment groups:
    - K-Lens in 1 eye and placebo lens in the other eye (N~40);
    - K-Lens in both eyes (N~40); or
    - Placebo lens in both eyes (N~40).
- At Visit 4, subjects were challenged with allergen 12 hours after lens insertion to evaluate the 12-hour duration of effect.
- At Visit 5, to test a 15-minute onset of action, subjects received the same randomized

treatment assigned at Visit 4 and were challenged with allergen 15 minutes after lens insertion.

Figure 1 – Diagram of Study Design for Phase 3 Efficacy Studies



Pre- and post-CAC evaluations were conducted, and lenses were removed. If subjects had any AEs, including but not limited to ocular events, they were scheduled to see the investigator for a follow-up visit. Safety was closely monitored throughout the trial by reviewing reports of adverse events (AEs), ocular and non-ocular, and by reviewing changes between the pre- and post-treatment ophthalmologic examinations using slit-lamp biomicroscopy (including corneal fluorescein staining), visual acuity (best-corrected and contact lens-corrected), and undilated fundoscopy.

Study Endpoints

Primary Efficacy Measure at 3-, 5-, and 7-minutes post CAC at Visits 4 and 5:

- Ocular itching scores were evaluated by the subject using a 0.5 increment scale of 0=none to 4.0=incapacitating itch with irresistible urge to rub.

Secondary Efficacy Measures at 7-, 15-, and 20-minutes post CAC at Visits 4 and 5:

- Ciliary hyperemia, conjunctival hyperemia, and episcleral hyperemia were evaluated by the investigator using a 0.5 increment scale where 0 = none and 4.0 = extremely severe;
- Chemosis was evaluated by the investigator using a 0.5 increment scale where 0 = none and 4.0 = extremely severe;
- Mucous discharge was evaluated by the investigator as present or absent;
- Tearing was evaluated by the subject as present or absent; and
- Lid swelling was evaluated by the subject using a scale where 0 = none and 3 = severe.

Safety Measures:

- Slit-lamp biomicroscopy (including corneal fluorescein staining) (Visits 1-5)
- Visual acuity (best-corrected and contact lens-corrected) (Visits 1-5)

- Undilated fundoscopy (Visits 4 and 5) and
- AEs (reported, elicited, and observed) (Visits 1-5)

Table 1 - Schedule of Visits and Assessments

ASSESSMENTS PERFORMED	STUDY PERIOD				
	Screening	Baseline		Double Masked Treatment[1]	
	Day-28 ± 3	Day-21 ± 3	Day-14 ± 3	Day 0	Day 14 ± 3
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed consent discussion and form	X				
Medical history and concomitant medication	X				
Medical history update		X	X	X	X
Demographic data	X				
Pregnancy test	X				X
Visual acuity	X	X	X	X	X
Spherocylindrical refraction	X				X
Keratometry	X				
Slit lamp examination[2]	X	X	X	X	X
Fluorescein staining	X	X	X	X	X
Ocular[3] allergic assessments	X	X	X	X	X
CAC titration without lenses	X				
CAC titration with lenses		X			
CAC confirmation with lenses			X		
Randomization				X	
K-Lens or placebo lens insertion[4]				X	X
Undilated fundoscopy				X	X
Adverse events[5]	X	X	X	X	X
CAC 12 hours after lens insertion				X	
CAC 15 minutes after lens insertion					X
Exit					X

1. Subjects were randomized at Visit 4 and received 1 test lens in each eye at Visits 4 and 5.
2. A slit lamp examination was performed to assess the health of the ocular surface and to grade allergic signs (hyperemia and chemosis). General ocular surface health was assessed at the beginning and at the end of each of the 5 visits. Assessments of the signs of ocular allergy were made at baseline of each visit and at the previously described times following challenge. Grading scales are provided in Appendix 16.1.1: Protocol, Appendix 1.
3. Allergic ocular symptoms (itching, lid swelling, and tearing) were assessed at the baseline slit lamp examination of each visit and at the previously described times following challenge.
4. Exposure for each treatment group was approximately 13 hours at Visit 4 and approximately 1 hour at Visit 5.
5. AEs reported both spontaneously and elicited were recorded on the CRF. If subjects reported an ocular AE after study exit then visual acuity, slit lamp, and undilated fundoscopy examinations were performed, as indicated. See Appendix 16.1.1.

Study Population

Inclusion Criteria

Subjects had to meet all of the following criteria in order to be enrolled into the trial:

1. Were able and willing to provide written informed consent/assent (approved by an IRB) prior to any study-specific evaluation;
2. Were able and willing to follow all study instructions;
3. Were at least 8 years of age, male or female of any race;
4. Were adequately fitted with 1•DAY ACUVUE® by an optometrist or ophthalmologist at Visit 1;
5. Had a Snellen Visual Acuity score of 20/30 or better in each eye at Visit 1 with spherocylindrical refraction;
6. Had a Snellen Visual Acuity score of 20/30 or better in each eye with 1•DAY ACUVUE® at Visit 1;
7. Had a correction from +6.00 to –12.00 diopters in each eye and astigmatism of -1.00 diopter or less in each eye;
8. 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;
9. 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;
10. Were able and willing to avoid all disallowed medications for the appropriate washout period (prior to Visit 1) and during the study trial period;
11. 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;
12. If female and of childbearing potential (those that are not surgically sterilized or post-menopausal), submitted a negative pregnancy test at Visits 1 and 5, and agreed to use an adequate method of birth control (spermicide with barrier; oral contraceptive; injectable, or implantable method of contraception; transdermal contraceptive; or intrauterine device; or, surgical sterilization of partner) for the duration of the study. For non-sexually active females, abstinence may have been regarded as an adequate method of birth control for the duration of the study.

Exclusion Criteria

Subjects were not enrolled in the study if they met any of the following criteria:

1. Had contraindications to the use of the test articles;
2. Had a known allergy to the test articles or their components;
3. If female, were pregnant, nursing or planning a pregnancy, or had a positive urine pregnancy test at Visit 1;
4. Had any ocular condition or preauricular lymphadenopathy that in the investigator's opinion could have affected the subject's health or the study parameters. This included, but was not limited to: clinically significant blepharitis, follicular conjunctivitis, pterygium, narrow angle glaucoma, or a diagnosis of dry eye.
5. Had active ocular infection (bacterial, viral, or fungal), or a positive history of ocular

herpetic infection;

6. Had previously had LASIK (laser-assisted in situ keratomileusis) surgery, photorefractive keratotomy (PRK), radial keratotomy (RK), neurotrophic keratitis, or a corneal transplant;
7. Had any ocular surgery within the past 6 months or anticipated having ocular surgery during the study;
8. Were concurrently enrolled or had participated in an investigational drug/device trial within 30 days of entering the study;
9. Had a medical condition that, in the investigator's opinion, could have affected study parameters, including but not limited to diabetes or the presence of any infectious or immunosuppressive disease;
10. Had moderate or above-normal corneal distortion by keratometry;
11. Had corneal staining scores ≥ 3 in either eye at the Visit 1 screening or subsequent baseline examinations.
12. Had hyperemia scores ≥ 2.0 in any vessel bed or any ocular itching in either eye at the baseline examination of any of the visits;
13. Used disallowed medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate pre-study washout period (prior to Visit 1) or planned to use such medications during the study. Contact lenses other than those provided at the study visits were not allowed. The appropriate pre-study washout period was as follows:
    a. H1 -antagonist antihistamines (including ocular): 72 hours;
    b. Corticosteroids or mast cell stabilizers (including ocular): 14 days;
    c. All other topical ophthalmic preparations other than the study drops: 72 hours, with the exception of rewetting drops, which may have been used up to 2 hours prior to each visit.

    Currently marketed OTC antihistamine/ vasoconstrictor combination eye drops may have been administered to subjects at the end of each visit, after all evaluations were completed.

Discontinued Subjects

Subjects could have voluntarily withdrawn from the study at any time. The investigator may have excluded or discontinued any subject for any sound medical reason. Subjects may have been discontinued before their completion of the study due to:

- An AE
- Protocol violations
- Administrative reasons (e.g., inability to continue, lost to follow up)
- Sponsor or investigator terminated study with notification
- Other

A contact lens-corrected visual acuity measurement of worse than 20/40 in either eye during the study could have resulted in the subject being discontinued.

Notification of a subject discontinuation and the reason for discontinuation was made to ORA and/or the study sponsor and was clearly documented on the subject's chart and CRF.

Study Treatments

- K-Lens (etafilcon A daily disposable contact lens with 0.019 mg ketotifen per lens)
- Placebo lens (etafilcon A daily disposable contact lens)

Adverse Events

All AEs either observed by the investigator or one of his/her medical collaborators, spontaneously reported by the subject, or in response to direct questioning, were noted on the AE page of the subject's CRF and in the source document. Only treatment-emergent AEs (defined as those occurring during or after the start of study treatment) were to be recorded as AEs.

STATISTICAL ANALYSIS PLAN

Analysis Populations

- Intent-to-Treat Population
  All randomized subjects who had at least 1 observation of the primary endpoint during the follow-up period (Visits 4 and 5). Primary analysis population.

- Per Protocol Population
  All ITT subjects who had no major protocol violations.

- Safety Population
  All randomized subjects who had at least 1 study lens inserted as recorded on the Study Lens Insertion portion of the CRF. All safety analyses were based on this safety population.

For the efficacy analyses, each eye was independently analyzed as a unit for comparison between the K-Lens and placebo lens treatments. In order to demonstrate efficacy at either Visit 4 or Visit 5, the primary efficacy endpoint values for K-Lens must have demonstrated superiority over the placebo lens by at least 0.5 units on a 0 to 4.0 scale for all time points tested, and at least 1 unit for the majority of time points.

The primary efficacy endpoint was ocular itching and was analyzed by using a 2-sample t-test for both Visit 4 and Visit 5. In addition, an analysis using the non-parametric Wilcoxon rank sum test, adjusting for centers for both Visit 4 and Visit 5 was performed. No adjustment for multiplicity was made.

A sample size of 240 eyes (approximately 120 subjects) was expected to have greater than 90% power to detect a difference in means of 1.0 (the difference between placebo lens mean ocular itching score of 2.0 and K-Lens mean ocular itching score of 1.0), assuming that the common standard deviation is 1.20 using a 2-sample t-test with an alpha of 0.050 at a 2-sided significance level. Demographic characteristics were compared using Analysis of Variance (ANOVA) tests for continuous measures and chi-square tests for categorical measures.

Secondary endpoints were analyzed with the same methods as the primary variables. For the safety evaluation, the incidence of subjects reporting any treatment-emergent AE or serious adverse event (SAE), including ocular and non-ocular AEs, was tabulated using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term for each treatment and overall, within each system organ class. The number of subjects reporting AEs was also summarized by severity of AEs and relationship to study medication. Visual acuity (best-corrected and contact lens corrected), slit-lamp evaluations, and undilated fundoscopy variables were descriptively summarized.

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. Changes in best-corrected visual acuity (spherocylindrical refraction) from baseline to Visit 5 were also measured in terms of number of lines of Snellen visual acuity. Frequency and percentages of abnormal changes in biomicroscopy from Visit 1 were summarized at each time point by treatment group.

Interim Analysis
No interim analysis was planned or conducted for either study.

6.1.2. Study CR-4483 Results

Compliance with Good Clinical Practices
All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

Clinical Study Report (CSR) Amendment Summary

Study CR-4483
The Clinical Study Report for Study CR-4483 was originally issued on March 14, 2008. The amendment was issued on April 20, 2012.

Study CR-4483, had 2 sites, Site 1, Eugene B. McLaurin, MD and Site 2, Fred Kurata, MD. During a post-study assessment, the sponsor 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. CR-4483 Clinical Study Report (CSR) was amended to include a site by treatment interaction data analysis.

To investigate potential differences in treatment response between sites, p-values corresponding to the type III sums of squares for treatment, site and treatment by site interaction from an ANOVA model were generated for each time point at each visit. The table

below details the results of the treatment by site interaction for each post allergen challenge time point at Day 0 and Day 14. The results did not demonstrate a treatment by site interaction for CR-4483; but the study was not sufficiently powered for this analysis. The difference between K-Lens and placebo was not clinically different between sites as shown at each site separately for each of the post allergen challenge time points.

Post Allergen Assessment	Treatment By Site Interaction (p-value[b])	Site 1: Difference[a] (p-value[c])	Site 2: Difference[a] (p-value[c])
Visit 4 (Day 0) 3 Min.	0.518	-1.153 (< 0.001)	-1.012 (< 0.001)
Visit 4 (Day 0) 5 Min.	0.803	-1.239 (< 0.001)	-1.183 (< 0.001)
Visit 4 (Day 0) 7 Min.	0.229	-0.975 (< 0.001)	-1.256 (< 0.001)
Visit 4 (Day 0) LOCF	0.229	-0.975 (< 0.001)	-1.256 (< 0.001)
Visit 5 (Day 14) 3 Min.	0.074	-1.322 (< 0.001)	-0.939 (< 0.001)
Visit 5 (Day 14) 5 Min.	0.719	-1.289 (< 0.001)	-1.207 (< 0.001)
Visit 5 (Day 14) 7 Min.	0.713	-1.183 (< 0.001)	-1.098 (< 0.001)
Visit 5 (Day 14) LOCF	0.713	-1.183 (< 0.001)	-1.098 (< 0.001)

[a] Difference = K-Lens minus Placebo; a negative difference favors K-Lens.
[b] ANOVA p-values corresponding to the type III sums of squares from model including treatment, site, and treatment by site interaction
[c] within subgroup p-value based on two-sample t-test for comparing K-Lens to Placebo
S t l 1

Reviewer's Comment: *The results of the Applicant's analysis did not show a site by treatment interaction and there is no evidence of bias from either site moderating the effect of treatment. Accordingly, the decision was made to keep the data from Site 1 in the primary efficacy analysis for CR-4483.*

Additionally, the following changes were also made to the CSR:

- Programming errors were identified and corrected which required modifications to tables and text in Section 2, 10.2, 12.5.2 and 14.1.
- Administrative changes to correct numerical calculations, rounding errors, incomplete table references and formatting.
- The List of Abbreviations and Definitions of Terms (Section 4) was updated in Section 4 and within the body of the report to accurately display all acronyms.

Patient Disposition

Table 6.1.2-1 - Subject Disposition

Parameter	Placebo /Placebo (N=40 n (%)	K-Lens /Placebo (N=41) n (n%)	K-Lens /K-Lens (N=39) n (n%)
ITT Population	40 (100)	41 (100)	39 (100)
Completed study	37 (92.5)	39 (95.1)	37 (94.9)
Per-protocol Population	36 (90.0)	37 (90.2)	37 (94.9)
Reasons for early discontinuation from the study	3 (7.5)	2 (4.9)	2 (5.1)
Subject choice	3 (7.5)	1 (2.4)	2 (5.1)
Other[a]	0	1 (2.4)	0
Lost to follow-up	0	0	0
Adverse event	0	0	0
Death	0	0	0

Source: Module 5.3.5.1, Study CR-4483 CSR. Section 14.1, Table 2 and Appendix 16.2, Listing 1.

[a] Subject (b) (6) was discontinued on Study Day 14 (Visit 5) due to a decrease in visual acuity that was considered not to be related to the test lens; the subject was using a placebo lens at the time when the test article was unmasked.

Protocol Violations

Table 6.1.2-2 - Protocol Violations (All Randomized Subjects)

Subject Number	Treatment Group	Violation
Investigator 1: Fred Kurata		
(b) (6)	PB/PB	Post-lens insertion VA assessed at 27 min. (should be 15 ±10 min)
	KLens/PB	Post-lens insertion VA assessed at 27 min. (should be 15 ±10 min)
	KLens/PB	Missing Itching scores at Visit 4 or 5.
Investigator 2: Eugene McLaurin		
(b) (6)	PB/PB	Missing Itching scores at Visit 4 or 5
	PB/PB	Missing Itching scores at Visit 4 or 5
	PB/PB	Missing Itching scores at Visit 4 or 5
	PB/PB	Missing Itching scores at Visit 4 or 5
	KLens/PB	Subject inserted -10D instead of -1.00D. Subject (b) (6) was not a screen fail. This subject completed Visit 5. Also, per a comment on page 24 of the source, the subject inadvertently inserted a -10.0D lens, but upon noting that the subject had the wrong power, a -1.0D lens was dispensed. The -10.0D lens was not dispensed.
	KLens/PB	Subject inverted (placed lens inside out) lens insertion (OD). Subject was only challenged in their left (OS) eye. Missing Itching scores at Visit 4 or 5.
	KLens/PB	Missing Itching scores at Visit 4 or 5.

(b) (6)	KLens/PB	Subject inverted (placed lens inside out) lens insertion (OS). Subject was only challenged in their right (OD) eye. Missing Itching scores at Visit 4 or 5.
	KLens/PB	Subject inserted both lenses in the wrong eyes. At the time, the decision was made to have the other test article inserted in the fellow eye with the intention to amend the original randomization scheme. However, since that time, it has been decided to not amend the original randomization scheme and for subject (b) (6) to be excluded from the "per protocol" population and final analysis.
	KLens/PB	Missing Itching scores at Visit 4 or 5.

Source: Module 5.3.5.1, Study CR-4483 CSR: Appendix 16.2, Listing 3.3.

Table 6.1.2-3 - Demographic and Baseline Characteristics (ITT Population)

Variable	Placebo /Placebo (N=40)	K-Lens /Placebo (N=41)	K-Lens /K-Lens (N=39)
Age (mean years ± SD)	29.0 ± 10.42	28.3 ± 7.30	29.5 ± 8.43
Min, Max	(15, 56)	(12, 49)	(16, 54)
Sex n (%)			
Female	21 (52.5)	19 (46.3)	21 (53.8)
Male	19 (47.5)	22 (53.7)	18 (46.2)
Race n (%)			
Caucasian	21 (52.5)	21 (51.2)	17 (43.6)
Asian	14 (35.0)	14 (34.1)	15 (38.5)
African American	4 (10.0)	4 (9.8)	5 (12.8)
American Indian or Alaska Native	1 (2.5)	1 (2.4)	1 (2.6)
Other	0	0	1 (2.6)
Native Hawaiian or Other Pacific Islander	0	0	0
Ethnicity n(%)			
Non-Hispanic	40 (100.0)	40 (97.6)	38 (97.4)
Hispanic	0	1 (2.4)	1 (2.6)
Iris Color n (%)			
Brown	22 (55.0)	25 (61.0)	30 (76.9)
Blue	9 (22.5)	7 (17.1)	5 (12.8)
Hazel	3 (7.5)	6 (14.6)	4 (10.3)
Green	6 (15.0)	3 (7.3)	0

Source: Module 5.3.5.1, Study CR-4483 CSR.: Section 14.1, Table 3.1

Reviewer's Comment: *Randomized subjects were predominantly white (49%), female (51%), and of non-Hispanic ethnicity (98%). The predominant iris color was brown (64%), followed by blue (18%). The treatment groups were well balanced.*

Table 6.1.2-4 - Baseline Snellen Visual Acuity and Slit Lamp Biomicroscopy (ITT Population)

	Placebo (N=121) n (%)	K-Lens (N=119) n (%)
Snellen Visual Acuity (Best Corrected)		
20/15	2 (1.7)	1 (0.8)
20/20	98 (81.0)	102 (85.7)
20/25	19 (15.7)	12 (10.1)
20/30	2 (1.7)	4 (3.4)
Slit Lamp Biomicroscopy		
No abnormal findings	104 (86.0)	101 (84.9)
No clinically significant findings	17 (14.0)	18 (15.1)
Clinically significant findings	0	0

Source: Module 5.3.5.1, Study CR-4483 CSR.: Section 14.1, Table 4.1

Reviewer's Comment: *At baseline, 84.6% of subject eyes had 20/20 or better best corrected visual acuity and 85.4% had no abnormal findings on slit lamp examination. There were no significant differences between placebo lens and K-Lens eyes.*

Table 6.1.2-5 - Selected Allergens Instilled in Eyes of 5% or More Subjects at Visit 1 (ITT Population)

Allergen	Placebo /Placebo (N=40)	K-Lens /Placebo (N=41)	K-Lens /K-Lens (N=39)
Kentucky Bluegrass	11 (27.5)	10 (24.4)	5 (12.8)
Meadow Fescue	11 (27.5)	4 (9.8)	9 (23.1)
Rye Grass	6 (15.0)	8 (19.5)	9 (23.1)
Bermuda Grass	5 (12.5)	6 (14.6)	1 (2.6)
Ragweed	2 (5.0)	4 (9.8)	5 (12.8)
Cat Dander	3 (7.5)	4 (9.8)	2 (5.1)
Cat Hair	1 (2.5)	2 (4.9)	4 (10.3)

Source: Module 5.3.5.1, Study CR-4483 CSR.: Section 14.1, Table 5.1

Prior and Concomitant Medications

Almost all subjects used Visine-A®/Naphcon-A® (naphazoline/pheniramine), a relief medication, in the study (99.2% overall [238/240]). At Visits 1 through 5, relief medication could have been administered after all CAC evaluations were completed, to relieve any ocular itching or hyperemia. No other ocular medications were used by more than 5% of subjects.

The use and types of prior and concomitant non-ocular medications were consistent with the subject population targeted by the inclusion/exclusion criteria and reflected in the demographic characteristics and medical histories. There were some imbalances among the treatment groups in the percentages of subjects taking medications in particular pharmacological classes; however, these differences were not assessed to be clinically meaningful. The most frequently taken medications, by 21.7% (26/120) of subjects overall, were in the therapeutic class of progestogens and estrogens, fixed combinations. The most frequently taken medication, by 14.2% (17/120) of subjects overall, was in the pharmacologic class paracetamol.

Efficacy Results – Primary Endpoint

Table 6.1.2-6 Summary (Continuous Analysis) of Ocular Itching at Visits 4 and 5 (ITT Population)

Visit Time point	Treatment [a] Placebo (N=121)	 K-Lens (N=119)	Difference[b]	P value[c]
Visit 4 (12 hour)	121	119		
Pre-Challenge Mean (SD)	0	0	0	
Post-Challenge	119	117		
3 Min Mean (SD)	1.71 (0.89)	0.61 (0.70)	-1.10	<0.001
5 Min Mean (SD)	1.96 (0.90)	0.74 (0.73)	-1.22	<0.001
7 Min Mean (SD)	1.86 (0.94)	0.79 (0.79)	-1.07	<0.001
Visit 5 (15 minute)	112	113		
Pre-Challenge Mean (SD)	0	0.01 (0.07)	0.01	0.158
3 Min Mean (SD)	1.60 (0.87)	0.42 (0.66)	-1.18	<0.001
5 Min Mean (SD)	1.82 (0.92)	0.56 (0.71)	-1.26	<0.001
7 Min Mean (SD)	1.69 (0.95)	0.54 (0.70)	-1.15	<0.001

Source data: Module 5.3.5.1, Study CR-4483 CSR Section 14.1, Table 6.1b

[a]Individual eye was the unit of analyses.

[b]Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used.

[c]*P* value was based on two-sample t-test comparing K-Lens to placebo. NC = not calculated.

Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the subject evaluated itching on the following 0 to 4 scale:
0 = None;
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye;
1.0 = An intermittent tickle sensation involving more than just the corner of the eye;
1.5 = Intermittent all-over tickling sensation;
2.0 = A mild continuous itch (could be localized) without desire to rub;
2.5 = Moderate, diffuse continuous itch with desire to rub;
3.0 = A severe itch with desire to rub;
3.5 = Severe itch improved with minimal rubbing; or
4.0 = Incapacitating itch with an irresistible urge to rub.

Reviewer's Comment:

A clinically and statistically significant reduction in ocular itching scores was achieved by the K-Lens treated eyes compared with placebo-treated eyes at both Visit 5, the onset of action (Visit 5, challenge at 15 minutes after lens insertion) and Visit 4, the duration of action (challenge at 12 hours after lens insertion) study visits.

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy was evaluated using the assessments made at 7, 15, and 20 minutes post CAC.

Table 6.1.2-7 Summary of Conjunctival Hyperemia at Visits 4 and 5 (ITT Population)

Visit Time point	Treatment [a] Placebo (N=121)	 K-Lens (N=119)	Difference[b]	P value[c]
Visit 4 (12 hour)				
N	121	119		
Pre-Challenge Mean (SD)	0.63 (0.36)	0.67 (0.37)	0.04	0.450
N	119	117		
7 Min Mean (SD)	1.51 (0.79)	1.27 (0.77)	-0.24	0.018
15 Min Mean (SD)	1.60 (0.81)	1.45 (0.83)	-0.15	0.155
20 Min Mean (SD)	1.62 (0.86)	1.53 (0.94)	-0.10	0.413
Visit 5 (15 minute)	112	113		
Pre-Challenge Mean (SD)	0.33 (0.33)	0.30 (0.31)	-0.03	0.465
7 Min Mean (SD)	1.56 (0.63)	1.15 (0.63)	-0.41	<0.001
15 Min Mean (SD)	1.67 (0.75)	1.34 (0.69)	-0.33	0.001
15 Min Mean (SD)	1.65 (0.81)	1.35 (0.77)	-0.30	0.004

Note: Module 5.3.5.1, Study CR-4483 CSR.: Section 14.1, Table 12b

[a] Individual eye was the unit of analyses.

[b] Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used.

[c] *P* value was based on 2-sample t-test comparing K-Lens to placebo.

Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the investigator evaluated ciliary hyperemia on a 0 to 4 scale, allowing for half increment scores, where 0=none, 1=mild, 2=moderate, 3 = severe, and 4 = extremely severe.

Reviewer's Comment: *The effect on hyperemia is minimal and not clinically relevant. The product will not be indicated in patients with eyes that are hyperemic.*

6.2. Study CR-4484 - A Multi-Center, Randomized, Double-Masked, Placebo-Controlled Evaluation of the Efficacy and Safety of K-Lens as Compared to Placebo Lens in the Prevention of Allergic Conjunctivitis in a Population of Allergic Contact Lens Wearers in the Conjunctival Allergen Challenge (CAC) Model

Reviewer's Comment: *The following Study Design section includes only information that is different between Study CR-4483 and Study CR-4484.*

6.2.1. Study Design

Refer to Section 6.1.1 for details.

Changes in the Conduct of the Study or Planned Analyses
One amendment was made to the protocol on January 16, 2007. Following is the Protocol Amendment Summary:

- To modify the nominal ketotifen concentration to 0.019 mg ketotifen per lens
- To modify the study design from single center to a multi-center
- To include up to three sites for the study design
- To modify inclusion criteria J to include up to October as part of ragweed season
- To modify the Visit 1 and Visit 3 day ranges

Snellen visual acuity (best corrected) and slit lamp biomicroscopy findings at baseline were analyzed using the Cochran-Mantel-Haenszel test.

6.2.2. Study CR-4484 Results

Refer to Section 6.1.2 for the Compliance with Good Clinical Practices statement and the Financial Disclosure statement.

<u>Study CR-4484</u>
There have been two amendments to the CR-4484 Clinical Study Report (CSR):

- Following database lock and completion of the final study report on March 14, 2008, a consultant for the sponsor on March 28, 2008 identified:
  - Several inconsistent values (including several dates and one visual acuity (VA) value) in the database for study CR-4484.
  - Three (3) additional listings which were not part of the original Statistical Analysis Plan (SAP)
  - Eight (8) listings which were updated in order to make necessary adjustments. Please see the Attachment 1: "Amendment to the Final Clinical Study Report" dated June 20, 2008 for additional information regarding the changes implemented to the CSR.

- The sponsor reviewed the CSR and identified additional amendments on December 7, 2011 that included:
  - Programming errors within the clinical database which required modifications to tables and text in Section 10.2, 12.5.2 and 14.1

- Administrative changes to correct numerical calculations, transcription errors, rounding errors, incomplete table references and formatting.
- Clarification of study information regarding:
  - The outcome of a subject's pregnancy
  - The reporting of ocular and non-ocular adverse events
  - See Attachment 2: "Amendment to the Final Clinical Study Report" dated February 08, 2012 for additional information regarding the changes implemented to the CSR.

Table 6.2.2-1 Subject Disposition

Parameter	Placebo/Placebo (N=42) n (%)	K-Lens/Placebo (N=41) n (n%)	K-Lens/K-Lens (N=41) n (n%)
ITT Population	42 (100)	41 (100)	41 (100)
Completed study	41 (97.6)	40 (97.6)	38 (92.7)
Per-protocol Population	41 (97.6)	38 (92.7)	37 (90.2)
Reasons for early discontinuation from the study	1 (2.4)	1 (2.4)	3 (7.3)
Other	1 (2.4)	0	2 (4.9)
Lost to follow-up	0	1 (2.4)	0
Adverse event[a]	0	0	1 (2.4)
Subject choice	0	0	0
Death	0	0	0

[a] Subject (b) (6) was withdrawn from the study for pregnancy.
Source: Mod 5.3.5.1, Study CR-4484 CSR Section 14.1, Table 2 and Appendix 16.2, Listing 1.

Reviewer's comment: *Ninety-six percent of subjects completed the study; 93.5% completed without major protocol violations/deviations. One subject was withdrawn from the study due to pregnancy. Subsequent medical reports were obtained. Medical follow-up revealed an uneventful pregnancy and delivery and healthy child born at term.*

Table 6.2.2-2 Selected Allergens Instilled in Eyes of 5% or More Subjects at Visit 1 (ITT Population)

Allergen	Placebo /Placebo (N=42)	K-Lens /Placebo (N=41)	K-Lens /K-Lens (N=41)	Overall (N=124)
Ragweed	11 (26.2)	11 (26.8)	12 (29.3)	34 (27.4)
Birch	10 (23.8)	5 (12.2)	6 (14.6)	21 (16.9)
Kentucky Bluegrass	8 (19.0)	5 (12.2)	5 (12.2)	18 (14.5)
Cat Dander	4 (9.5)	6 (14.6)	3 (7.3)	13 (10.5)
Rye Grass	3 (7.1)	3 (7.3)	6 (14.6)	12 (9.7)
Meadow Fescue	1 (2.4)	2 (4.9)	8 (19.5)	11 (8.9)
Cat Hair	2 (4.8)	6 (14.6)	1 (2.4)	9 (7.3)

Source: Mod. 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 5.1

Protocol Violations/Deviations
18 protocol violations

Table 6.2.2-3 - Protocol Violations (All Randomized Subjects)

Subject Number	Treatment Group	Violation
Investigator 2: Gail Torkildsen		
(b) (6)	PB/PB	Subject refitted with different lens Rx than previously fitted at Visit 1
	PB/PB	Post-lens insertion VA assessed at 27 min. (should be 15 ±10 min)
	KLens/KLens	Subject was not challenged at 1 dose lower at Visit 2
	PB/KLens	Missing Itching scores at Visit 4 or 5.
Investigator 3: Edward Meier		
(b) (6)	KLens/KLens	Missing Itching scores at Visit 4 or 5.
	KLens/KLens	Missing Itching scores at Visit 4 or 5.
Investigator 4: Thomas Macejko		
(b) (6)	PB/PB	Minor subject was consented at V1, however, inadvertently did not sign assent. Subject signed the assent at V2.
	KLens/KLens	Subject had inverted the right (OD) test lens upon insertion. Subject removed OD test lens and test lens was inventoried. Subject was only challenged in the left (OS) eye.
		Subject was only tested OS which was the only eye wearing a test lens.
		Missing Itching scores at Visit 4 or 5.
	PB/KLens	Subject took disallowed medication (Benadryl) the morning of Visit 4 prior to receiving the test lenses. Subject did not report this until the evening of Visit 4 at the part 2 of the visit.
	PB/KLens	Subject was unable to return to the evening portion of Visit 4 and did not complete Visit 4. (Test lenses were removed and saved for inventory on (b) (6) Subject returned for follow-up on Monday, (b) (6) and returned the worn test lenses).
		Subject dropped worn test lens from her right (OD) eye into the sink. Used test lens was inventoried and a 1-Day Acuvue was dispensed. Subject was only challenged in her Left (OS) eye.
		Missing Itching scores at Visit 4 or 5.
Investigator 5: Mark Bergmann		
(b) (6)	PB/PB	Missing Itching scores at Visit 4 or 5
	PB/PB	Minor subject was consented at V1, however, inadvertently did not sign assent. Subject signed the assent at V2.
	KLens/KLens	Missing Itching scores at Visit 4 or 5
	PB/KLens	Subject did not have a post-CAC visual acuity performed

Source: Module 5.3.5.1, Study CR-4484 CSR, Appendix 16.2, Listing 3.3.

Table 6.2.2-4 Demographic and Baseline Characteristics (ITT Population)

Variable	Placebo /Placebo (N=42)	K-Lens /Placebo (N=41)	K-Lens /K-Lens (N=41)
Age (mean years ± SD)	29.6 ± 11.61	29.4 ± 12.86	29.7 ± 11.40
Minimum, maximum	(13, 61)	(13, 57)	(13, 60)
Sex n (%)			
Female	26 (61.9)	23 (56.1)	25 (61.0)
Male	16 (38.1)	18 (43.9)	16 (39.0)
Race n (%)			
Caucasian	30 (71.4)	31 (75.6)	30 (73.2)
Asian	11 (26.2)	9 (22.0)	10 (24.4)
Other	1 (2.4)	1 (2.4)	1 (2.4)
Ethnicity n (%)			
Non-Hispanic	40 (95.2)	39 (95.1)	39 (95.1)
Hispanic	2 (4.8)	2 (4.9)	2 (4.9)
Iris color n (%)			
Brown	19 (45.2)	18 (43.9)	22 (53.7)
Blue	13 (31.0)	13 (31.7)	8 (19.5)
Hazel	5 (11.9)	4 (9.8)	7 (17.1)
Green	5 (11.9)	5 (12.2)	4 (9.8)
Other	0	1 (2.4)	0

Source data: Module 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 3.1

Reviewer's comment: *The majority of study subjects were non-Hispanic Caucasian females and approximately 30 years of age.*

Table 6.2.2-5 Baseline Snellen Visual Acuity and Slit Lamp Biomicroscopy (ITT Population)

	Placebo (N=125) n (%)	K-Lens (N=123) n (%)	Overall (N=248) n (%)
Snellen Visual Acuity (Best Corrected)			
20/20	104 (83.2)	98 (79.7)	202 (81.5)
20/25	18 (14.4)	22 (17.9)	40 (16.1)
20/30	3 (2.4)	3 (2.4)	6 (2.4)
Slit Lamp Biomicroscopy			
No abnormal findings	103 (82.4)	105 (85.4)	208 (83.9)
No clinically significant findings	22 (17.6)	18 (14.6)	40 (16.1)
Clinically significant findings	0	0	0

Source data: Module 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 4.1

Efficacy Results – Primary Endpoint

Table 6.2.2-7 Summary (Continuous Analysis) of Ocular Itching at Visits 4 and 5 (ITT Population)

Visit	Treatment[a]			
Time point	Placebo (N=125)	K-Lens (N=123)	Difference[b]	*P* value[c]
Visit 4 (12 hour)				
Pre-Challenge				
n	125	123		
Pre-Challenge Mean (SD)	0.00 (0.00)	0.00 (0.00)		
n	124	121		
3 Min Mean (SD)	1.80 (0.89)	0.75 (0.83)	-1.05	< 0.001
5 Min Mean (SD)	2.04 (0.89)	0.88 (0.91)	-1.16	< 0.001
7 Min Mean (SD)	1.99 (0.89)	0.86 (0.91)	-1.13	< 0.001
Visit 5 (15 minute)				
n	124	120		
Pre-Challenge Mean (SD)	0.02 (0.13)	0.04 (0.32)	0.03	0.418
n	121	116		
3 Min Mean (SD)	1.72 (0.94)	0.42 (0.61)	-1.30	< 0.001
5 Min Mean (SD)	1.94 (0.91)	0.56 (0.72)	-1.38	< 0.001
7 Min Mean (SD)	1.83 (0.98)	0.59 (0.80)*	-1.24	< 0.001

Source: Module 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 6.1b.

* N=114

a Individual eye was the unit of analyses. b Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used. c P value was based on two-sample t-test comparing K-Lens to placebo. NC = not calculated.
Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the subject evaluated itching on the following 0 to 4 scale: 0 = None;
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye;
1.0 = An intermittent tickle sensation involving more than just the corner of the eye;
1.5 = Intermittent all-over tickling sensation;
2.0 = A mild continuous itch (could be localized) without desire to rub;
2.5 = Moderate, diffuse continuous itch with desire to rub;
3.0 = A severe itch with desire to rub;
3.5 = Severe itch improved with minimal rubbing; or
4.0 = Incapacitating itch with an irresistible urge to rub.

Reviewer's comment*: In order to demonstrate clinical efficacy, treatment group differences of at least 25% of the scale were demonstrated at the majority of time points evaluated. The study demonstrated clinical efficacy for K-Lens for the prevention of ocular itching.*

Efficacy Results – Secondary and other relevant endpoints

Table 6.2.2-9 Summary of Conjunctival Hyperemia at Visits 4 and 5 (ITT Population)

Visit Time point	Treatment [a]		Difference [b]	*P* value [c]
	Placebo (N=125)	K-Lens (N=123)		
Visit 4 (12 hour)				
Pre-Challenge				
n	125	123		
Pre-Challenge Mean (SD)	0.48 (0.43)	0.46 (0.46)	-0.03	0.660
n	124	121		
7 Min Mean (SD)	1.83 (0.75)	1.38 (0.76)	-0.45	< 0.001
15 Min Mean (SD)	2.02 (0.72)	1.72 (0.77)	-0.30	0.002
20 Min Mean (SD)	2.00 (0.74)	1.71 (0.82)	-0.29	0.004
Visit 5 (15 minute)				
n	124	120		
Pre-Challenge Mean (SD)	0.55 (0.46)	0.46 (0.49)	-0.09	0.142
n	121	116		
7 Min Mean (SD)	2.09 (0.72)	1.51 (0.79)	-0.58	< 0.001
15 Min Mean (SD)	2.30 (0.71)	1.81 (0.79)	-0.49	< 0.001
20 Min Mean (SD)	2.30 (0.69)	1.76 (0.83)	-0.54	< 0.001

Source: Module 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 10b.

[a]Individual eye was the unit of analyses. [b]Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used. [c]P value was based on 2-sample t-test comparing K-Lens to placebo.

Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the investigator evaluated conjunctival hyperemia on a 0 to 4 scale, allowing for half increment scores, where 0=none, 1=mild, 2=moderate, 3=severe, and 4=extremely severe.

Reviewer's comment*: Clinical efficacy was not demonstrated because treatment group differences of at least 25% of the scale were not demonstrated at any of time points evaluated.*

K-Lens does not meet this definition of efficacy for conjunctival hyperemia, ciliary hyperemia, episcleral hyperemia, or chemosis. In addition, K-Lens is not indicated for hyperemic eyes.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The results of the Phase 3 conjunctival allergen challenge (CAC) studies, CR-4483 and CR-4484, were consistent, demonstrating efficacy for the prevention of itching. There were no differences based on age, race, or gender.

7.1.1. Dose and Dose-Response

Not studied.

7.1.2. Onset, Duration, and Durability of Efficacy Effects

In both studies, the mean itching scores were statistically significantly lower ($p<0.001$) for subjects wearing K-Lens at both onset (within 3 minutes) and at 12 hours after administration.

7.2. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen).

8. Review of Safety

8.1. Safety Review Approach

This review of the safety data will focus on the Phase 3 Pool (N=804) which includes data from all subjects who wore a test lens(es) at least once in at least 1 eye in the Phase 3 conjunctival antigen challenge (CAC) Studies CR-4483, CR-4484, or in the Phase 3 Studies CR-4490 and CR-4539. Pooled data from all 4 studies, provided the safety analysis set for the proposed commercial K-Lens dosage.

Data Excluded from Study CR-4490, Site 3

Upon review of the documentation for each clinical study, the Sponsor discovered a high number of corrections to the subject dispensing log for Site 3 from Study CR-4490 that made it difficult to ensure that subjects received the appropriate test lenses. For this reason, analyses of TEAEs and VA were performed including and excluding data from this study site for both the Phase 3 Pool and the Long-term Safety Pool.

Of the 310 randomized and treated subjects in Study CR-4490, Site 3 contributed data from 69 subjects (22.2% of the total study safety population). There were 46 subjects in the K-Lens group and 23 subjects in the placebo lens group, all of whom completed the 12-week study.

4 Month Safety Update

On August 19, 2021, (SDN-9) the 4-month Safety Update (4MSU) Report was submitted. There have been no complaints, adverse events, risk control measures, or new or additional safety findings within April 30, 2021 through June 30, 2021 time period. No new data which may affect safety performances were found. A literature review identified no new safety information. The safety information for the ACUVUE® Theravision™ with Ketotifen remains consistent with the original NDA and with the Integrated Summary of Safety (ISS) in Module 5.3.5.3 of the original NDA.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across all 13 studies, 1,258 subjects were exposed to test lenses, 833 (66.2%) of whom were exposed to K-Lens 25. Of the 833 subjects exposed to K-Lens 25, 349 subjects (41.9%) wore the lenses for >60 to 91 days.

Table 8.2.1-1: Summary of Exposure to K-Lens 25 (0.019 mg/lens) Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	Total (N=735)
Total Number of Subjects Exposed to K-Lens 25	490 (66.7%)
< 8 hours	1 (0.2%)
1-3 days	160 (32.7%)
> 3 – 14 days	2 (0.4%)
>14 – 30 days	5 (1.0%)
> 30 – 60 days	14 (2.9%)
> 60 -91 days	304 (62.0%)
Missing	4 (0.8%)

Source data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFEXP06
Note: Percentages are based the total number of subjects exposed to K-Lens 25.
Each day of exposure is considered individually and only days that had exposure of ≥ 8 hours are counted as a day.

Reviewer's Comment: *The safety database is considered adequate.*

8.2.2. Relevant characteristics of the safety population:

Table 8.2.2-1 Demographics Safety Population Excluding Data from Site 3 from Study 4490(Ph 3 Pool)	K-Lens 25/ K-Lens 25 (N=408)	K-Lens/ Placebo (N=82)	Placebo/Placebo (N=245)
Age (years)			
N	408	82	245
Mean (SD)	31.4 (11.87)	28.9 (10.41)	29.9 (10.82)
Median	29.0	26.5	27.0
Min, Max	11, 62	12, 57	13, 66
Age Group			
<18	49 (12.0%)	12 (14.6%)	27 (11.0%)
18 – 40	266 (65.2%)	58 (70.7%)	179 (73.1%)
> 40	93 (22.8%)	12 (14.6%)	39 (15.9%)
Sex			
Male	128 (31.4%)	40 (48.8%)	90 (36.7%)
Female	280 (68.6%)	42 (51.2%)	155 (63.5%)
Race			
White	307 (75.2%)	52 (63.4%)	183 (74.7%)
Black or African American	65 (15.9%)	4 (4.9%)	30 (12.2%)
Asian	31 (7.6%)	23 (28.0%)	27 (11.0%)
American Indian or Alaska Native	1 (0.2%)	1 (1.2%)	1 (0.4%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	4 (1.0%)	2 (2.4%)	4 (1.6%)
Ethnicity			
Hispanic or Latino	6 (1.5%)	3 (3.7%)	5 (2.0%)
Not Hispanic or Latino	402 (98.5%)	79 (96.3%)	240 (98.0%)
Iris Color			
Blue	101 (24.8%)	20 (24.4%)	68 (27.8%)
Brown	197 (48.3%)	43 (52.4%)	112 (45.7%)
Green	49 (12.0%)	8 (9.8%)	31 (12.7%)

Hazel	61 (15.0%)	10 (12.2%)	34 (13.9%)
Other	0	1 (1.2%)	0

Note: Percentages are based on the number of subjects in each treatment group.
Source: Integrated Summary of Safety, Table TSIDEM11

Reviewer's Comment: *The safety population is representative of the population that the drug product is intended to treat.*

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

AEs were classified by MedDRA system organ class (SOC) 20.1.

8.3.3. Routine Clinical Tests

Refer to Section 8.4.6.

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the clinical development of the product.

8.4.2. Serious Adverse Events

In the Phase 3 Pool excluding Study CR-4490, Site 3, nine subjects (0.9%) in the K-Lens 25/K-Lens 25 group experienced SAEs. These were abdominal discomfort, cholelithiasis, facial bones fracture and benign adenoma, each of which occurred in 1 subject (0.3%). No SAEs occurred in the placebo/placebo group.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 8.4.3-1: Incidence of Ocular Treatment Emergent Adverse Events Leading to Study Medication Discontinuation, Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25	Placebo	Total
Number of Eyes in Safety Population	898	572	1470
Total Number of Ocular Adverse Events Leading to Study Medication Discontinuation	8	5	13
Number of Eyes with at Least One Ocular Adverse Event Leading to Study Medication Discontinuation	4 (0.4%)	5 (0.9%)	9 (0.6%)
Infections and infestations	1 (0.1%)	4 (0.7%)	5 (0.3%)
Conjunctivitis	1 (0.1%)	2 (0.3%)	3 (0.2%)
Conjunctivitis viral	0	2 (0.3%)	2 (0.1%)
Eye disorders	2 (0.2%)	1 (0.2%)	3 (0.2%)
Dry eye	2 (0.2%)	0	2 (0.1%)
Eye irritation	2 (0.2%)	0	2 (0.1%)
Eye pruritus	2 (0.2%)	0	2 (0.1%)
Ocular discomfort	0	1 (0.2%)	1 (0.1%)
Injury, poisoning and procedural complications	1 (0.1%)	0	1 (0.1%)
Corneal abrasion	1 (0.1%)	0	1 (0.1%)

Note: Percentages are based on the number of eyes in each treatment group.
Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization.
At each level of summarization, an eye is counted once if the eye reported one or more events.
Source Data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFAE076

Table 8.4.3-2:
Incidence of Non-Ocular Treatment Emergent Adverse Events Leading to Study Medication Discontinuation by Preferred Term Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25/ K-Lens 25 (N=408)	K-Lens 25/ Placebo (N=82)	Placebo/ Placebo (N=245)	Total (N=735)
Total Number of Non-Ocular Adverse Events Leading to Study Medication Discontinuation	5	0	2	7
Number of Eyes with at Least One Non-Ocular Adverse Event Leading to Study Medication Discontinuation	4 (1.0%)	0	2 (0.8%)	6 (0.8%)
Abdominal discomfort	1 (0.2%)	0	0	1 (0.1%)
Cholelithiasis	1 (0.2%)	0	0	1 (0.1%)
Facial bones fracture	1 (0.2%)	0	0	1 (0.1%)

Adenoma benign	1 (0.2%)	0	0	1 (0.1%)
Headache	0	0	1 (0.4%)	1 (0.1%)
Complication of pregnancy	1 (0.2%)	0	0	1 (0.1%)
Upper airway cough syndrome	0	0	1 (0.4%)	1 (0.1%)

Note: Percentages are based on the number of eyes in each treatment group.
Adverse events are coded using MedDRA version 20.1.
Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization.
At each level of summarization, a subject is counted once if the subject reported one or more events.
Source Data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFAE086

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.4-1: Incidence of Ocular Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25	Placebo
Number of Eyes in Safety Population	898	572
Total Number of Ocular Adverse Events	92	15
Number of Eyes with at Least One Ocular Adverse Event	68 (7.6%)	13 (2.3%)
Eye disorders	51 (5.7%)	8 (1.4%)
Eye irritation	14 (1.6%)	0
Eye Pain	10 (1.1%)	0
General disorders and administration site conditions	16 (1.8%)	2 (0.3%)
Instillation site pain	12 (1.3%)	1 (0.2%)

Note: Percentages are based on the number of eyes in each treatment group. Adverse events are coded using MedDRA version 20.1.
Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization.
At each level of summarization, an eye is counted once if the eye reported one or more events.
Source Data: Module 5 3.5.3; Integrated Summary of Safety, Table TSFAE048

Table 8.4.4-2: Incidence of Non-Ocular Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25/K-Lens 25 (N=408)	K-Lens 25/Placebo (N=82)	Placebo/Placebo (N=245)
Total Number of Non-Ocular Adverse Events	107	11	50
Number of Eyes with at Least One Non-Ocular Adverse Event	77 (18.9%)	9 (11.0%)	36 (14.7%)
Infections and infestations	40 (9.8%)	0	8 (3.3%)
Nasopharyngitis	10 (2.5%)	0	2 (0.8%)
Sinusitis	9 (2.2%)	0	1 (0.4%)
Urinary Tract Infection	4 (1.0%)	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	11 (2.7%)	7 (8.5%)	8 (3.3%)
Epistaxis	0	1 (1.2%)	0
Nasal congestion	2 (0.5%)	1 (1.2%)	2 (0.8%)
Oropharyngeal pain	3 (0.7%)	2 (2.4%)	2 (0.8%)
Respiratory tract congestion	0	1 (1.2%)	0
Rhinorrhea	0	2 (2.4%)	1 (0.4%)

Sinus congestion	0	1 (1.2%)	0
Sinus disorder	3 (0.7%)	0	3 (1.2%)
Injury, poisoning and procedural complications	11 (2.7%)	0	5 (2.0%)
Procedural pain	6 (1.5%)	0	0
Nervous system disorders	4 (1.0%)	3 (3.7%)	6 (2.4%)
Headache	2 (0.5%)	3 (3.7%)	3 (1.2%)
Vascular disorders	5 (1.2%)	0	2 (0.8%)
Hypertension	5 (1.2%)	0	2 (0.8%)

Note: Percentages are based on the number of subjects in each treatment group. Adverse events are coded using MedDRA version 20.1.
Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization. At each level of summarization, a subject is counted once if the subject reported one or more events.
Source Data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFAE058

8.4.5. Vital Signs -Not performed.

8.4.6. Electrocardiograms (ECGs) -Not performed.

8.4.7. QT - Not applicable.

8.4.8. Immunogenicity – Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Visual Acuity

Table 13: Summary of Line Changes [1] from Baseline to Last Visual Acuity Scores — Best-Corrected; Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25	Placebo
Number of Eyes in Safety Population	898	572
Line Changes		
>= 3 Lines Increase	0	0
>= 2 to < 3 Lines Increase	0	0
>= 1 to < 2 Lines Increase	13 (1.4%)	5 (0.9%)
< 1 Line Increase or Decrease	869 (96.8%)	556 (97.2%)
>= 1 to < 2 Lines Decrease	0	0
>= 2 to < 3 Lines Decrease	0	0
>= 3 Lines Decrease	0	0
Missing	16 (1.8%)	11 (1.9%)

Note: Percentages are based on the number of eyes in each treatment group.
[1] Line change = 10 x [- log (20/dfollow-up) — (- log (20/dbaseline))], where dfollow-up is the denominator of the Snellen fraction at the last visit and dbaseline is the denominator of the Snellen fraction at baseline. A line increase (i.e., positive line change) indicates a worsening of visual acuity and a line decrease (i.e., negative line change) indicates an improvement of visual acuity.
Source Data: Mod5.3.5.3/ISS/LSFVA01

Reviewer's Comment: *No study participants experienced clinically significant changes in visual acuity with the use of K-Lens.*

8.6. Safety Analyses by Demographic Subgroups

Adverse event and VA analyses defined by age, gender, race and iris color were evaluated. The results for each subgroup were consistent with the overall safety profile. No clinically relevant or unexpected ocular or non-ocular AEs were identified, and the use of K-Lens 25 did not appear to negatively affect VA.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development – Not conducted.

8.7.2. Human Reproduction and Pregnancy – Not conducted.

8.7.3. Pediatrics and Assessment of Effects on Growth

In the Phase 3 Studies CR-4490, CR-4539, CR-4483, and CR-4484, subjects as young as 8 years old were eligible for enrollment. The youngest subjects enrolled were 11 years old. Across the Phase 3 studies, 92 subjects <18 years of age were enrolled and wore at least 1 test lens for at least 1 day, of whom 63 were exposed to K-Lens 25. All but 1 subject (exposed to K-Lens 25) of the 92 pediatric subjects completed the study treatment period including 42 subjects exposed to K-Lens 25, who completed 12 weeks of treatment in the Phase 3 long-term safety studies. One pediatric subject in study CR-4539 was discontinued from the study due to a randomization error.

The safety profile (AEs or VA) for K-Lens 25 among pediatric subjects was not different from that of older subjects. No additional clinical studies are planned with K-Lens 25 in subjects younger than 11 years of age.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Ketotifen fumarate is not a narcotic and does not have any abuse potential.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

On August 19, 2021 (SDN-9) the 4-month Safety Update (4MSU) Report was submitted. Since the commercial launch in Canada, on May 10, 2021, an estimate of (b) (4) boxes ((b) (4) lenses) were dispensed to (b) (4) patients. No complaints have been received since the commercial launch. A second commercial launch was initiated in Japan, on June 25, 2021. An estimate of (b) (4) boxes (b) (4) lenses) were dispensed to (b) (4) patients. No complaints have been received since the commercial launch.

There have been no complaints, adverse events, risk control measures, or new or additional safety findings within April 30, 2021 through June 30, 2021 time period. No new data which may affect safety performances were found. A literature review identified no new safety information. The safety information for the ACUVUE® Theravision™ with Ketotifen remains consistent with the original NDA and with the Integrated Summary of Safety (ISS) in Module

5.3.5.3 of the original NDA.

8.8.2. Expectations on Safety in the Postmarket Setting – Not applicable.

8.9. Integrated Assessment of Safety

The data contained in this original NDA establishes the safety of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for the correction of ametropia 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 astigmatism.

9. Advisory Committee Meeting and Other External Consultations

There were no issues identified during the review of this NDA that required an Advisory Committee discussion.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling recommendations are provided in track changes in the draft revised Package Insert, Patient Instruction Guide, and Carton and Container labeling in the Appendix 13.3 at the end of this review.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. Financial Disclosure

Clinical Investigator Financial Disclosure

Review Template

Application Number: NDA 22388
Submission Date(s): April 30, 2021
Applicant: Johnson and Johnson Vision Care, Inc.
Product: ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen)

Reviewer: Rhea A. Lloyd, MD
Date of Review: August 10, 2021
Covered Clinical Studies (Name and/or Number):

CR-4483
CR-4484
CR-4490
CR-4539

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of principal investigators identified: CR-4483 2 investigators, 6 sub-investigators CR-4484 6 investigators, 8 sub-investigators CR-4490 3 investigators, 16 sub-investigators CR-4539 1 investigator, 3 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): CR-4483 None. CR-4484 None. CR-4490 1 investigator CR-4539 None.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

From Attachment A – Form FDA 3455
DISCLOSURE: Financial Interests and Arrangements of Clinical Investigators

(b) (6), MD participated as a sub investigator in the below listed covered clinical study.

Covered Clinical Study: Study (b) (6)
A phase 3, multicenter, double-masked, randomized, parallel group, bilateral eye, placebo-controlled study to evaluate the safety and tolerability of K-Lens compared with placebo lens.
Principal Investigator: (b) (6)

Disclosure statement:
Dr. (b) (6) reported significant equity interest in the corporate parent of the sponsor, i.e., Johnson and Johnson stock valued at approximately $50,000.

Potential bias of the clinical study results for the study is mitigated by the fact that:
- The studies were double masked and involved multiple subinvestigators. In addition, the study involved multiple sites as well as multiple investigators, from which the data was pooled. Data from this study was pooled across investigators.
- Neither Vistakon Pharmaceuticals, LLC, the sponsor of the study, or its immediate parent, Johnson & Johnson Vision Care, Inc., are themselves publicly traded corporations. Potential revenue from this K-Lens product would represent only a very small portion of the Johnson & Johnson portfolio within its family of companies.

13.2. Draft Labeling

It is recommended that the application be approved with these draft labeling changes. See CDTL review for all final labeling.

18 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RHEA A LLOYD
02/23/2022 08:12:45 AM

WILLIAM M BOYD
02/23/2022 08:22:56 AM