SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: omafilcon A soft (hydrophilic) contact lens

Device Trade Name: MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear

Device Procode: QIT

Applicant's Name and Address: CooperVision, Inc.
5870 Stoneridge Drive
Pleasanton, CA 94588

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P180035

Date of FDA Notice of Approval: November 15, 2019

II. INDICATIONS FOR USE

MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear are indicated for the correction of myopic ametropia and for slowing the progression of myopia in children with non-diseased eyes, who at the initiation of treatment are 8-12 years of age and have a refraction of -0.75 D to -4.00 D (spherical equivalent) with ≤ 0.75 diopters of astigmatism. The lens is to be discarded after each removal.

III. CONTRAINDICATIONS

Do not use the MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear when any of the following conditions exist:

- Acute and subacute inflammation or infection of the anterior chamber of the eye.
- Any eye disease, injury, or abnormality that affects the cornea, conjunctiva, or eyelids.
- Severe insufficiency of lacrimal secretion (dry eyes).
- Corneal hypoesthesia (reduced corneal sensitivity), if not aphakic.
- Any systemic disease that may affect the eye or be exaggerated by wearing contact lenses.
- Allergic reactions of ocular surfaces or adnexa that may be induced or exaggerated by wearing contact lenses or use of contact lens solutions.
- Any active corneal infection (bacterial, fungal, or viral).
- If eyes become red or irritated.
- The patient is unable to follow lens handling and wear regimen or unable to obtain assistance to do so.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear labeling.

V. DEVICE DESCRIPTION

MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear are made from a material containing 60% water and 40% omafilcon A, consisting of 2-hydroxy-ethylmethacrylate and 2-methacryloyloxyethyl phos-phorycholine polymers cross-linked with ethyleneglycol dimethacrylate. The lens material has a permanently fixed tint using Vat Blue 6, which is added to make the lens more visible for handling.

MiSight daily wear single use finished contact lenses parameters:

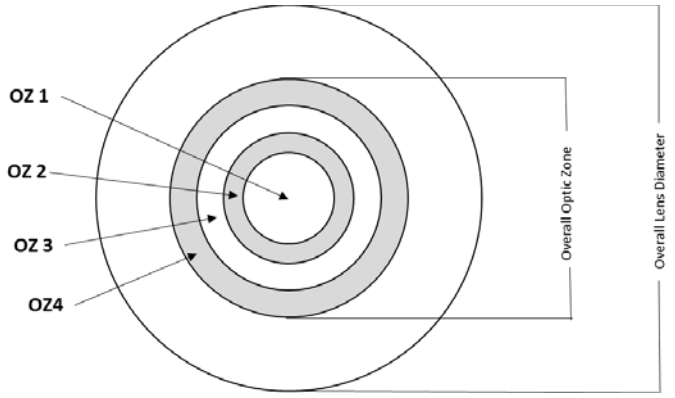
- Diameter: 13.00 mm to 15.5 mm
- Basic Curve: 8.00 mm to 9.50 mm
- Center Thickness: 0.08 mm to 0.14 mm (dependent on power)
- Powers: -0.50D to -7.00D in 0.25 steps
- Refractive Index: 1.400 ± 0.005 at 25˚C
- Edge Thickness 0.070 ± 0.020 mm
- Packaging Solution – pH 7.4 ± 0.6
- Osmolality 305 ± 55 mOsm/Kg

MiSight daily wear single use contact lenses physiochemical and mechanical properties:

- Oxygen Permeability (Dk): 25×10^{-11} (cm^2/sec) x (ml O_2)/(ml x mm Hg)
- Water content: 60% w/w
- Light Transmittance: ≥ 90 % at 500 nm

The optic zone design is a concentric ring design with alternating vision correction zones and treatment zones (shaded in diagram). Zones 1 and 3 are vision correction zones and the label power of the contact lens. Zones 2 and 4 are treatment zones with 2 diopters of defocus to slow the progression of myopia.

Figure 1: MiSight Optical Design



Batches of individual blisters are injection molded from polypropylene material with aluminium foil laminate. A lens is inserted in each blister cavity and the packing solution (phosphate-buffered saline with Tween 80) is added, then the foil is sealed. The finished strips of blisters are then packaged into printed cartons.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no other approved contact lenses (or other FDA-approved treatments) for slowing the progression of myopia in children. There are many alternatives for the optical correction of myopia, including conventional soft or rigid contact lenses, as well as spectacles, which are widely available.

VII. MARKETING HISTORY

The MiSight 1 Day (omafilcon A) Soft (Hydrophilic) Contact Lenses for Daily Wear is currently approved in the following markets: Australia, Canada, EU (CE marking), Hong Kong, Singapore. The MiSight lens has not been withdrawn from marketing in any market for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device: corneal infection, corneal ulcer/opacity, infiltrative keratitis, corneal abrasion, corneal edema, neovascularization, iritis, conjunctivitis, giant papillary conjunctivitis, blepharitis/meibomianitis, tarsal hyperemia/lid irritation, hyperemia of the bulbar conjunctiva, superficial punctate keratitis, subconjunctival hemorrhage, and mild pannus.

Additional specific adverse reactions that may occur include the following:

- Eyes stinging, burning, or itching (irritation), or other eye pain.
- Comfort is less than when the lens was first placed on the eye.
- Feeling that something is in the eye such as a foreign body or a scratched area.
- Excessive watering (tearing) of the eyes.

- Unusual eye secretions.
- Redness of the eyes.
- Reduced sharpness of vision (poor visual acuity).
- Sensitivity to light (photophobia).
- Dry eyes.

Due to the optical design of the MiSight lenses, containing two focal points, under certain circumstances (e.g., low light conditions) some wearers may notice reduced image contrast, halos or glare around bright lights or ghost images (double images).

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The lens material used in MiSight lens is the same as Proclear Daily Disposable Contact lens (omafilcon A) cleared by FDA (K061948) and already on the market since clearance in 2006. Many of the preclinical studies were conducted for the Proclear Daily Disposable contact lens and therefore, where applicable, were not repeated for MiSight, as it is the same material (omafilcon A). Tests included analysis of extractable residual components, characterization of physical and chemical properties, toxicology, microbiology, and shelf life stability. A summary of test results is shown below.

A. Laboratory Studies

1. Biocompatiblity

   Non-clinical testing was conducted to verify safety of the MiSight (omafilcon A) Soft contact lens. Non-clinical biocompatibility testing was conducted in accordance with FDA's *Premarket Notification 510(k) Guidance Document for Daily Wear Contact Lenses,* May 1994 and GLP regulation (21 CFR part 58).

   Non-clinical testing performed includes:

   - Biocompatibility testing per ISO 10993-5, ISO 10993-10, ISO 10993-11, and ISO 9394

   All test results met the pre-established acceptance criteria.
   The testing performed on the MiSight (omafilcon A) Soft contact lens demonstrates the lens is safe. Non-clinical testing included conformance to predetermined specifications.

Table 1: Biocompatibility – MiSight (omafilcon A) Soft contact lens

Test Method	Acceptance Criteria	Results
Cytotoxicity – ISO Agarose Overlay ISO 10993-5:2009	≤ grade 2 (mild reactivity)	The test article showed no evidence of causing cell lysis or toxicity.
Ocular Irritation –in rabbits ISO 10993-10:2002	If the test extract showed no significant irritation over the reagent control during the observation period.	There was no evidence of significant irritation in the test eye or control eye of any animal. The test article extracts were not considered irritants to the ocular tissue of the rabbit.
22 Day Ocular Irritation ISO 9394:1998	Macroscopic ocular reaction grades (Draize scoring). Biomicroscopic slit lamp data were evaluated in accordance with McDonald-Shadduck criteria. Lactic acid data were compared between groups to determine biological relevance.	Macroscopically, eyes treated with test lens were similar to the untreated eyes. Microscopically, there was no evidence of ocular irritation or toxicity in test eyes from application of the test lens. The test and control values obtained for the corneal lactic acid data were similar and differences were not considered biologically significant.

Acute Systemic Toxicity in mice ISO 10993-11:2006	None of the animals treated with the individual test extract exhibited a significantly greater reaction than the control animals, the test articles met the requirements of the standard. If two or more animals died, or if abnormal behavior such as convulsions or prostration occurred in two or more animals, or if body weight loss greater than 2 grams occurred in three or more animals, the test article did not meet the test requirements.	There was no mortality or evidence of systemic toxicity from the extracts. All animals appeared clinically normal throughout the study. Body weight data were acceptable. Both test article and extracts met the test requirements.

The MiSight (omafilcon A) Soft contact lenses are packaged in a polypropylene blister pack containing phosphate-buffered saline with Tween 80. The packaging materials and solution were subjected to cytotoxicity, systemic toxicity and ocular irritation testing. A summary of the testing is provided below:

Table 2: Biocompatibility – MiSight (omafilcon A) Soft contact lens packaging solution

Test Method	Acceptance Criteria	Results
Cytotoxicity – MEM ISO Elution Method ISO 10993-5:2009	≤ grade 2 (mild reactivity)	The test article showed no evidence of causing cell lysis or toxicity.
Ocular Irritation – in rabbits ISO 10993-10:2010	If the test eye in more than one animal showed a positive irritant response, the test article is considered an ocular irritant. A severe reaction in only one animal is considered to be sufficient evidence to label the test article as an ocular irritant.	There was no irritation observed in the treated eyes as compared to the untreated control eyes. The test article would not be considered an irritant to the ocular tissue of the rabbit.
ISO Systemic Toxicity Study in mice - Solution ISO 10993-11:2006	None of the animals treated with the individual test extract exhibited a significantly greater reaction than the control animals, the test articles met the requirements of the standard. If two or more animals died, or if abnormal behavior such as convulsions or prostration occurred in two or more animals, or if body weight loss greater than 2 grams occurred in three or more animals, the test article did not meet the test requirements.	There was no mortality or evidence of systemic toxicity from the test article. All animals were clinically normal throughout the study. The test article met the test requirements.

Table 3: Biocompatibility – MiSight (omafilcon A) Soft contact lens packaging material

Test Method	Acceptance Criteria	Results
Cytotoxicity – MEM ISO Elution Method ISO 10993-5:1999	≤ grade 2 (mild reactivity)	The test article showed no evidence of causing cell lysis or toxicity.
Ocular Irritation – in rabbits ISO 10993-10:2010	No significant irritation over the reagent control during the observation period.	There was no evidence of significant irritation in the test eye or control eye of any rabbit. The test article would not be considered an irritant to the ocular tissue of the rabbit.
ISO Systemic Toxicity Study - Extract in mice ISO 10993-11:2006	None of the animals treated with the individual test extract exhibited a significantly greater reaction than the control animals, the test articles met the requirements of the standard. If two or more animals died, or if abnormal behavior such as convulsions or prostration occurred in two or more animals, or if body weight loss greater than 2 grams occurred in three or more animals, the test article did not meet the test requirements.	There was no mortality or evidence of systemic toxicity from the extracts. All animals appeared clinically normal throughout the study. Body weight data were acceptable. Both test article extracts met the test requirements.

2. Physicochemical Tests

Physicochemical tests were performed to demonstrate long term safety and stability of the properties of the material used to manufacture the MiSight (omafilcon A) Soft contact lens. See the following table for a summary of results.

Table 4: Physicochemical testing – MiSight (omafilcon A) Soft contact lens

Test	Purpose	Acceptance Criteria	Results
Preservative Uptake and Release	To determine the preservative uptake and release of the contact lens material	N/A	This testing is not required for MiSight Contact Lenses as they are daily disposable and should be removed and discarded after each day of wear.
Compatibility with Lens Care Products	To determine compatibility of contact lens care products with contact lenses	N/A	This testing is not required for MiSight Contact Lenses as they are daily disposable.
Extractables – Leachability	To determine if any tint leached out during extraction with phosphate buffered saline	N/A	No detectable levels of tint were found in any of the phosphate buffered saline leachates.
Extractables - Soxhlet Extraction	The quantity of extractables from the Soxhlet extraction	N/A	The extractables ranged from 1.6 - 1.7% for water and 1.3 - 1.7% for n-hexane

Table 5: Laboratory Results

Physical and chemical properties	
Refractive index	1.400
Oxygen permeability, Dk, (cm2/sec) x (mlO_2)/(mlO_2)/(mlx mmHg)	25×10^{-11}
Water content	60% w/w
Light transmittance (%)	≥ 90 % at 500 nm
Shelf Life	5 years

Shelf life studies for parameter stability over time indicate no change to measured parameters from baseline over the storage period.	

3. Sterilization, Bioburden, and Shelf Life

The MiSight (omafilcon A) Soft contact lenses are provided in a polypropylene blister and sealed with aluminum foil laminate. The packaging solution is a sterile phosphate -buffered saline with Tween 80. The packaged lenses are steam sterilized using a validated sterilization process. Each lens is labeled with the lens parameters, lot number and expiration date and placed in boxes with appropriate labeling.

Routine bioburden testing is performed prior to sterilization. This testing provides an assessment of the cleanliness of the devices being manufactured and the facility in general. The bioburden test method was validated in accordance with ISO Standard 11737-1:2006, "Sterilization of health care products – Microbiological methods – Part 1: Determination of the population of microorganisms on product."

The MiSight (omafilcon A) Soft contact lens are terminally sterilized by subjecting the finished device to moist heat sterilization. The moist heat sterilization cycle was validated using the overkill method (full cycle approach) in accordance with Annex D of ISO Standard 17665-1:2006, "Sterilization of health care products –Moist heat – Part 1: Requirements for the development, validation and routine control of sterilization process for medical devices." The sterilization process for the device was validated to achieve a Sterility Assurance Level (SAL) of 10^{-6}.

Shelf life studies have been conducted to verify that the packaging for the MiSight (omafilcon A) Soft contact lens maintains a sterile barrier and adequately protects the device through the expiration date on the package label, which is 5 years. Shelf life testing has also been conducted to verify that device physical and optical properties meet the product specifications through the 5 year labeled expiration date. All test samples satisfied all acceptance criteria (see **Table 4**).

Table 6: Sterility, Bioburden, and Shelf Life

Test	Purpose	Acceptance Criteria	Results
Bioburden testing	Evaluate the cleanliness of the manufacturing process and facility	Vegetative growth: Alert: > 900 CFU/device Action: >1,000 CFU/device Spores/Molds/Anaerobes: Action: ≤10 CFU/device	Pass

Moist Heat Sterilization Validation	Evaluate sterility	No positive biological indicators	Pass
Package Evaluation – Dye Penetration Testing	Evaluate whole package integrity	No evidence of dye across seal by a defined channel	Pass
Sterility testing, USP<71> – Direct inoculation method	Evaluate sterility	Negative for growth	Pass
Shelf-life	To establish the expiration date	Finished Product Specifications	5 years

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study to establish a reasonable assurance of safety and effectiveness of contact lens wear with the MiSight (omafilcon A) daily wear single use soft contact lenses for the optical correction of myopia and for slowing the progression of myopia in children aged 8 – 12 years , with refraction of -0.75 D to -4.00 D of myopia, at the initiation of treatment. The study was conducted outside of the U.S (in Canada, Singapore, Portugal, and the United Kingdom), and was not conducted under an IDE.

In addition, the applicant performed a retrospective data audit to study the rate of microbial keratitis in children wearing conventional soft daily wear contact lenses. This study was conducted at community clinics in the U.S. evaluating records of children fit at ages 8 – 12 at the time of initial fitting.

Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

1. MiSight Randomized Controlled Study (MIST-401)

A. Study Design

Patients were treated between November 2012 and February 2017. The database for this PMA reflected data collected through February 2017, and included 187 enrolled patients (with 144 randomized and 135 dispensed lenses). The lenses were worn on a daily disposable basis. There were 4 investigational sites.

The study was a 3-year, multi-center, prospective, parallel group, 2-armed, randomized, controlled, double-masked clinical study. Frequentist statistical analysis was used to test the hypotheses. For effectiveness, the hypotheses tested were that the increase from

baseline to the 3-year visit in mean cycloplegic autorefractor spherical equivalent refractive error (SERE) and in mean ocular axial length were each significantly less in the MiSight arm than in the control (conventional soft contact lens) arm. The statistical analysis used a linear mixed model, statistically adjusting for possible baseline imbalances in age, sex, ethnicity, or baseline refractive error. Randomization (1:1) was stratified by clinical center and age group using a random permuted block design stratified by investigational site. Sample size calculations were based on an assumption of 0.75 D difference compared to the control group after 3-years. The protocol anticipated an enrollment target of 150 eligible subjects per arm to account for 40 % screen failures, and a 14% attrition rate per year.

The control group wore the Proclear 1 Day (omafilcon A) daily disposable soft contact lens. The control lens was identical to the MiSight lens with the exception of the front surface optical design as described in Section V above.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the MIST-401 study was limited to patients who met the following inclusion criteria:

   1. Be between 8 and 12 years of age inclusive at the baseline examination.
   2. Have:
      a. read the Informed Assent,
      b. been explained the Informed Assent,
      c. indicated an understanding of the Informed Assent and
      d. signed the Informed Assent Form.
   3. Have their parent or legal guardian:
      a. read the Informed Consent,
      b. been given an explanation of the Informed Consent,
      c. indicated an understanding of the Informed Consent and
      d. signed the Informed Consent Form.
   4. Along with their parent or guardian, be capable of comprehending the nature of the study, and be willing and able to adhere to the instructions set forth in this protocol.
   5. Along with their parent or guardian, agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study (see Visit Schedule, Section 3.5).
   6. Agree to accept either the control or test lens as assigned by the randomization scheme.
   7. Agree to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the 3-year study and to inform the study investigator if this schedule is interrupted. (Wearing time may be modified by the study staff for health reasons.)
   8. Possess wearable and visually functional eyeglasses.
   9. Be in good general health, based on his/her and parent's/guardian's knowledge.
   10. Have best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25 Snellen equivalent) or better in each eye.

11. Meet the following refractive criteria determined by cycloplegic autorefraction at baseline:
    a. Spherical Equivalent Refractive Error (SERE): between -0.75 and -4.00 D inclusive.
    b. Astigmatism: -0.75 D
    c. Anisometropia: < 1.00 D

Subjects were not permitted to enroll in the MIST-401 study if they met any of the following exclusion criteria:

1. Subject has previously worn, or currently wears contact lenses or rigid gas permeable contact lenses, including orthokeratology lenses.
2. Subject appears to exhibit poor personal hygiene (that in the investigator's opinion might prevent safe contact lens wear).
3. Subject is currently or within 30 days prior to this study has been an active participant in another clinical study.
4. Parent/ guardian or close relative is a member, of the office staff, including the investigator(s).
5. Current or prior use of bifocals, progressive addition lenses, atropine, pirenzepine or ANY other myopia control treatment.
6. Subject was born earlier than 30 weeks or weighed less than 1500g (3.31b) at birth.
7. Regular use of ocular medications (prescription or over-the-counter), artificial tears, or wetting agents.
8. Current use of systemic medications which may significantly affect contact lens wear, tear film production, pupil. size, accommodation or refractive state. Such as, but not limited to: long term use of nasal decongestants (for example, pseudoephedrine, phenylephrine), antihistamines (for example, chlorpheniramine, diphenhydramine), Prednisolone or Ritalin (methylphenidate).
9. A known allergy to fluorescein, benoxinate, proparacaine or tropicamide.
10. A history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, ocular viral or fungal infections or other recurrent ocular infections.
11. Strabismus by cover test at far (4 m) or near (40 cm) wearing distance correction.
12. Known ocular or systemic disease such as, but not limited to: anterior uveitis or iritis, episcleritis or scleritis, glaucoma, Sjogren's syndrome, lupus erythematosus, scleroderma, or diabetes.
13. Any ocular, systemic or neuro-developmental conditions that could influence refractive development. Such as, but not limited to: persistent pupillary membrane, vitreous hemorrhage, cataract, corneal scarring, ptosis eyelid hemangiomas, Maran’s Syndrome, Down's syndrome, Ehler's-Danlos syndrome, Stickler's syndrome, ocular albinism, retinopathy of prematurity.
14. Keratoconus or an irregular cornea.

15. Biomicroscope findings that would contraindicate contact lens wear including, but not limited to:
    a. corneal scars within the visual axis
    b. neovascularization or ghost vessels 1.5 mm in from the limbus
    c. Any active anterior segment ocular disease that would contraindicate contact lens wear.
    d. giant papillary conjunctivitis of Grade 2 or worse
    e. allergic or seasonal conjunctivitis (if the study investigator believes it could significantly interfere with maintaining the specified contact lens wearing schedule)
    f. clinically significant (Grade 3 or 4) abnormalities of the anterior segment, lids, conjunctiva, sclera or associated structures.
16. The investigator for any reason considers that it is not in the best interest of the subject to participate in the study.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations per the following schedule.

Table 1: Follow-up Schedule

Scheduled Follow-up Visits	Acceptable Range
Dispensing and I&R training	1-7 days from Baseline
1-week	7 days ± 2 days from dispensing
1 month	30 days ± 4 days from dispensing
6 months	180 days ± 7 days from dispensing
12 months	360 days ± 14 days from dispensing
18 months	540 days ± 21 days from dispensing
24 months	720 days ± 30 days from dispensing
30 months	900 days ± 37 days from dispensing
36 months	1080 days ± 44 days from dispensing

Pre-dispensing, evaluations included: case history, habitual visual acuity, non-cycloplegic autorefraction, keratometry , manifest refraction, best-corrected visual acuity, cover test, stereo acuity, ocular dominance test, binocular accommodative amplitude, biomicroscopy, pupil diameter, cycloplegic autorefraction, ophthalmoscopy, and parental questionnaire.

At dispensing, contact lens visual acuity, contact lens over-refraction, biomicroscopy, and lens fit evaluation were performed.

Post-dispensing, the same evaluations as performed at dispensing were repeated, and investigators also collected, wearing time, symptoms and subjective findings at every visit. Cycloplegic auto-refraction and axial length were measured at

baseline and annually thereafter. See the schedule of procedures, below. Adverse events and complications were recorded at all visits.

Table 2: Procedure Schedule

PROCEDURES	BASELINE	DISPENSE	FOLLOW UP VISITS								
		Day 0	1Wk	1 Mo	6 Mo	12 Mo	18 Mo	24 Mo	30 Mo	36 Mo	UNSCHED*
Informed Consent and Assent	X										
Case History	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications review	X	X	X	X	X	X	X	X	X	X	X
Lensometry	X									X	
Habitual VA (distance and near)	X	X								X	X (or pinhole distance)
Subject Non-Cycloplegic Autorefraction	X				X	X	X	X	X	X	
Keratometry	X					X		X		X	
Manifest subjective refraction	X				X	X	X	X	X	X	X
Best corrected VA (distance and near)	X					X		X		X	
Cover test (distance and near), PD and AC/A ratio	X									X	
Stereo acuity	X									X	
Ocular dominance	X										
Binocular accommodative amplitude	X					X		X		X	
NPC	X									X	
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X
Randomization	X										
CL corrected VA (distance and near)		X	X	X	X	X	X	X	X	X	
Contact lens over-refraction		X	X	X	X	X	X	X	X	X	
Lens fit assessment		X	X	X	X	X	X	X	X	X	
Optical aberrations with study lenses (or trial frame at baseline)	X			X	X	X	X	X	X	X	
Pupil diameter (mesopic and photopic with accommodation)	X			X	X	X	X	X	X	X	
Accommodative lag with trial frame	X					X		X		X	
Residual accommodation	X					X		X		X	
Cycloplegic auto-refraction	X					X		X		X	
Cycloplegic biometry (axial length)	X					X		X		X	
Binocular indirect ophthalmoscopy	X					X		X		X	
Parental questionnaire of child's daily activities	X		X	X	X	X	X	X	X	X	
Subject questionnaire			X	X	X	X	X	X	X	X	
Contact lens insertion and removal training / review		X	X	X	X	X		X			
Distribute Study Lens Patient Instructions		X									
Dispense study lenses and complete Lens Accountability Form		X	X	X	X	X	X	X	X		
Complications & Adverse Events	Complete where applicable										
Study Exit Form (and collect unused study supplies)	At 36 month if subject successfully completes the study, or when applicable if subject discontinues										
Parent/Guardian Informed Consent	X										
Biological Parent Non-Cycloplegic Autorefraction	X										

* minimum required for unscheduled problem visits
At the dispensing visit, schedule follow-up visit dates for at least the first 6-months to aid compliance.
Confirm the visit dates at each follow-up

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was the comparison of objective findings, including biomicroscopic findings and adverse events, between the test lens and the control lens. The protocol secondary safety endpoint was incidence of visual disturbances graded "very annoying" or "annoying" on the questionnaire used in the study. However, FDA review found that the questionnaires used by the applicant were not supported by any development data. This lack of evidence of questionnaire psychometric validity means that this data is potentially biased, and has substantial uncertainty.

With regards to effectiveness, the co-primary endpoints to assess myopic progression were changes from baseline to 3-years in:

- Mean cycloplegic Spherical Equivalent Refractive Error (SERE), and
- Mean axial length,

compared between the test and control groups.

Other key effectiveness outcomes included contact lens visual acuity, and wearing time.

With regard to success/failure criteria: The protocol did not have any definition of individual subject success. The protocol stated that, for the refractive effectiveness endpoint, a statistical difference will be concluded if the entire 95% confidence interval of the difference between arms in the mean SERE increase (baseline to 3-years) is greater than zero; a clinically significant difference will be concluded if the entire confidence interval is ≥0.75 D. For the axial length endpoint, the protocol stated that a statistical difference will be concluded if the entire 95% confidence interval on the difference between arms in mean axial length increase is less than zero.

B. Accountability of PMA Cohort

The protocol anticipated an enrollment target of 150 eligible subjects per arm to account for 40 % screen failures, and a 14% attrition rate per year. Due to a longer than expected recruitment period, it became evident that the number of subjects enrolled would be smaller than this target, and a review indicated that the actual number of subjects enrolled would be adequate. The total enrollment was 187 subjects, of whom 144 were randomized to MiSight or control lenses. Sixty-five (65) subjects were dispensed the MiSight lens and 70 subjects were dispensed the control lens. One hundred and eight patients (75% of those randomized) were available for analysis at the completion of the study, at the three-year post dispensing visit.

Table 3: Subject Accountability

	Control		MiSight		Total	
	N = 74	**%**	**N**	**%**	**N**	**%**
Enrolled (n)					**187**	**100**
Ineligible at Baseline (n)					**43**	**23.0**
Discontinued before randomization (n)					43	23.0
Eligible at Baseline / Randomized (n)	**74**	**100**	**70**	**100**	**144**	**77.0**
Dispensed Lenses (n)	70	94.6	65	92.9	135	72.2
Completed Study Visits & Exited (n)	**56**	**75.7**	**53**	**75.7**	**109**	**58.3**
Discontinued (n)	14	18.9	12	17.1	26	13.9
Not Dispensed (n)	4	5.4	5	7.1	9	4.8

% = n/N(100)

Those subjects not dispensed lenses were primarily due to unacceptable lens fit or difficulty handling lenses.

The primary reasons for discontinuation after dispensing included subject disinterest or dissatisfaction with lens wear. Only one of the discontinuations from MiSight was vision related. A small percentage of subjects were lost to follow up over the course of the 3-year study. Reasons for discontinuation are shown in the following table.

Table 4: Reasons for Discontinuations (All Randomized Subjects)

	Control (N= 74)		MiSight (N = 70)		Total (N = 144)	
	n	**%**	**n**	**%**	**n**	**%**
Not dispensed - Lens fit or handling	4	5.4	5	7.1	9	6.3
Adverse event	1	1.4	1	1.4	2	1.4
Intolerance/Discomfort/Dissatisfaction	3	4.1	2	2.9	5	3.5
Unsatisfactory vision	0	0.0	1	1.4	1	6.9
New medication	1	1.4	1	1.4	2	1.4
Inconvenience / Disinterest	4	5.4	4	5.7	8	5.6
Lens handling difficulties	2	2.7	1	1.4	3	2.1
Lost to follow-up	3	4.1	2	2.9	5	3.5

% = n/N(100)

All available data from all subjects were used in the statistical analyses.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are not fully typical of soft contact lens users in the U.S. (The study was conducted completely out of the U.S.). There was a substantially higher percentage of Asians in this study than in the U.S. population. However, Asians have a higher prevalence of myopia than do non-Asians, and this device is intended for myopic children. Therefore, perhaps a more important comparison is the proportion of myopes in the U.S. that are Asian. The applicant provided information from a published paper (Kleinstein RN, et al.) on the prevalence of myopia in various ethnic groups. This information, along with recent U.S. Census Bureau data on the proportion of Asians in the U.S., implies that the proportion of Asians among myopes in the U.S. population may be on the order of 17%, making the demographics of the study somewhat less of an issue. There is some uncertainty in this estimate. Therefore, one of the conditions of approval is that the applicant is to confirm the effectiveness results in a post-approval study conducted in the U.S. population.

Table 5: Subject Demographics (All Randomized Subjects)

	Control (N = 74)	**MiSight (N = 70)**
Age		
Mean ± SD	10.1 ± 1.3	10.1 ± 1.4
8-10 years old	42 (57%)	40 (57%)
11-12 years old	32 (43%)	30 (43%)
Sex		
Female	37 (50%)	38 (54%)
Male	37 (50%)	32 (46%)
Ethnicity		
Caucasian (European)	40 (54%)	39 (56%)
East Asian	18 (24%)	16 (23%)
Indian/ Pakistani/ Sri Lankan	7 (9%)	5 (7%)
Other	4 (5%)	2 (3%)
Mixed	5 (7%)	8 (11%)

% = n/N(100); SD – standard deviation

Table 6: Baseline SERE and Axial Length (All Randomized Subjects)

	Control (N = 148 eyes)	**MiSight (N = 140 eyes)**
Cycloplegic SERE		
Mean ± SD (D)	-2.19 ± 0.81	-2.02 ± 0.77
Maximum myopia (D)	-4.00	-3.75
Minimum myopia (D)	-0.83	-0.77
Axial Length		
Mean ± SD (mm)	24.5 ± 0.70	24.4 ± 0.66
Maximum (mm)	27.0	26.0
Minimum (mm)	23.0	22.7

SD – standard deviation

The two arms of the study were well balanced in terms of demographics and baseline refractive error and age.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the dispensed cohort of 135 subjects: 65 MiSight subjects and 70 Control subjects, through the 3-year study, with 52 MiSight subjects and 56 control subjects completing the entire follow-up.

The key safety outcomes for this study are presented below in Tables 7 to 9. Adverse effects are reported in Table 8.

Biomicroscopy Findings

Overall, there were very few visits (scheduled and unscheduled) with Grade 2 or greater biomicroscopy findings (Table 7). There were no Grade 4 findings and very few subject-visits with Grade 3 findings (0.4% MiSight; 0.1% Control).

Table 7: Visits with Biomicroscopy Findings (All Visits - Scheduled and Unscheduled)

	Control (N=1354 visits)	**MiSight** (N=1268 visits)
	n (%)	n (%)
Corneal ulcer	0 (0.0)	0 (0.0)
Corneal infiltrate	3 (0.2)	1 (0.1)
Corneal staining ≥ Grade 2	11 (0.8)	26 (2.1)
Corneal vascularization ≥ Grade 2	0 (0.0)	0 (0.0)

Bulbar hyperemia ≥ Grade 2	19 (1.4)	11 (0.9)
Limbal hyperemia ≥ Grade 2	3 (0.2)	5 (0.4)
Palpebral roughness ≥ Grade 2	22 (1.6)	46 (3.6)
Palpebral hyperemia ≥ Grade 2	47 (3.5)	66 (5.2)
Other Finding ≥ Grade 2	6 (0.4)	1 (0.1)

% = n/N(100)

Adverse effects that occurred in the PMA clinical study:

The incidence of adverse events was similar between the MiSight and Control lens groups. None of the ocular adverse events were considered to be serious adverse events.

Over the course of 3-years, there were 18 ocular adverse events reported in 11 subjects wearing the MiSight lens, 7 were lens-related, 1 was a mild infiltrative event. There were 12 ocular adverse events reported in 10 subjects wearing the Control lens, 6 were lens-related, 3 were mild infiltrative events (in 2 subjects). The table below summarizes the adverse events over the 3-year study.

Table 8: Eyes with Adverse Events (Eyes of All Dispensed Subjects) (All Available Eyes)

	Control (N = 140 eyes)		**MiSight (N =130 eyes)**	
	n	**%**	**n**	**%**
Infiltrative Keratitis	3	2.1	1	0.8
Corneal opacity	1	0.7	0	0.0
Conjunctivitis	3	2.1	2	1.5
Blepharitis / Meibomianitis	0	0.0	4	3.1
Tarsal hyperemia / Lid irritation	1	0.7	3	2.3
Foreign body	0	0.0	1	0.8
Superficial Punctate Keratitis	1	0.7	3	2.3
Subconjunctival hemorrhage	1	0.7	1	0.8
Mild pannus	0	0.0	1	0.8
Other: headache, asthenopia, dryness	2	1.4	2	1.5

% = n/N(100)

Best-Corrected Spectacle Acuity

The mean best corrected spectacle distance and near visual acuity was similar for the MiSight group and the Control group at baseline and at the 36-month visit.

The mean best corrected spectacle visual acuity for the two groups was within one letter of each other at each follow-up visit.

The clinical results in this study indicated that both arms had no serious adverse events and very low incidence of clinically significant slit lamp biomicroscopy observations. In addition, there were no clinically significant losses in best corrected acuity. FDA review concluded that this study raised no significant safety issues.

Table 9: Best Corrected Spectacle Visual Acuity (logMAR)

	Control		**MiSight**	
	Baseline (N=148)	36-Month (N=112)	Baseline (N=140)	36-Month (N=104)
Best Corrected Distance VA	-0.03 ± 0.06	-0.08 ± 0.05	-0.01 ± 0.05	-0.07 ± 0.06
Best Corrected Near VA	-0.06 ± 0.10	-0.11 ± 0.07	-0.05 ± 0.09	-0.11 ± 0.08

There were 2 cases of temporary reduction in visual acuity of two lines measured at one visit only. These were not related to any observation of significant eye problems and resolved without treatment.

2. Effectiveness Results

The analysis of effectiveness was based on the eligible, dispensed cohort of 135 subjects, 109 who completed the 3-year study: 53 MiSight subjects and 56 Control subjects. One MiSight subject was excluded from the 36-month effectiveness analysis because he had started growth hormone therapy in the last six months of the study. Key effectiveness outcomes are presented in Tables 10 to 15.

Cycloplegic Spherical Equivalent Refractive Error (SERE): 3-Year Change

The mean change in cycloplegic SERE was compared between the two groups using a linear mixed model, statistically adjusting for possible baseline imbalances in age, sex, ethnicity, or baseline refractive error. The least-squares-mean cycloplegic refractive error change over 3-years are shown below. Over the 3-year study, the MiSight arm had a lower increase in mean myopic SERE than the control by 0.67 D, with a 95% confidence interval (CI) of (0.49 to 0.84 D).

Table 10: 3-Year Change in Cycloplegic Spherical Equivalent Refractive Error (SERE) from Baseline

(LS Mean - All Available Eyes)

	LS Mean	Std. Err	95% Confidence Interval	p-value
Refractive Error (SERE)				
MiSight	-0.65 D	0.07	-0.50 to -0.79	
Control	-1.31 D	0.08	-1.16 to -1.46	
Difference	0.67 D	0.09	0.49 to 0.84	<0.0001

Axial Length: 3-Year Change

The mean change in axial length was compared between the two groups using a linear mixed model, statistically adjusting for possible baseline imbalances in age, sex, ethnicity, or baseline refractive error. The least-squares-mean axial length change over 3-years are shown below. Over the 3-year study, the MiSight arm had a lower increase in mean axial length than the control by 0.28 mm, with a 95% confidence interval of (0.20 to 0.36 mm).

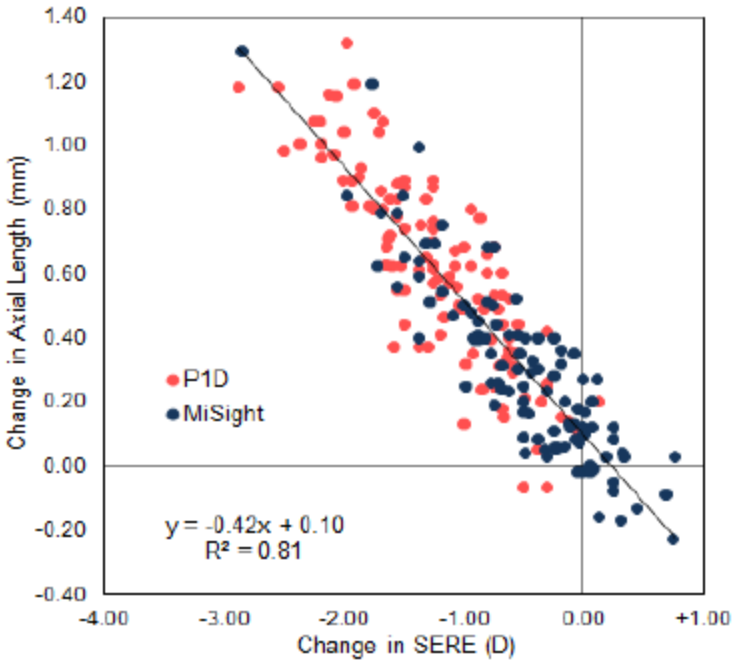
Table 11: 3-Year Change in Axial Length from Baseline
(LS Mean - All Available Eyes)

	LS Mean	Std. Err	95% Confidence Interval	p-value
Axial Length				
MiSight	0.34 mm	0.03	0.27 to 0.41	
Control	0.62 mm	0.03	0.56 to 0.69	
Difference	-0.28 mm	0.04	-0.20 to -0.36	<0.0001

Refractive Error and Axial Length Correlation

Correlations between change in axial length and change in SERE were tested using Pearson's coefficient showing statistically significant correlations at each of the follow-up visits for both groups. This indicates that a reduced SERE progression correlates with reduced rate of axial elongation. The MiSight and Control lens combined data at 3 years is shown in the figure below ($p<0.0001$).

Figure 1: Correlation between Change in SERE and Axial Elongation



Additional Analyses of Myopic Progression

Additional analyses were performed to further characterize the myopia progression in the two groups. The table below shows the percentage of subjects in each group at various levels of myopic increase from baseline to the final 3-year visit.

Table 12: 3-Year Cycloplegic SERE Change from Baseline

(All Available Eyes)

Change from Baseline	Control (N=112 eyes)		MiSight (N=104 eyes)	
	n	%	n	%
-0.25 D or less	4	3.6%	43	41.3%
-0.50 D or less	11	9.8%	57	54.8%
-0.75 D or less	30	26.8%	70	67.3%
-1.00 D or less	43	38.4%	85	81.7%
More than -1.00D	69	61.6%	19	18.3%

% = n/N(100)

The year-by-year change in refractive error is shown in the following table. This table shows the unadjusted mean change for all eyes with data within the interval as well as stratification by age at enrollment. In all age groups, the first year of use showed the greatest difference in myopia progression between test and control groups.

Table 13: Year-to-Year Cycloplegic SERE Change
(Unadjusted Mean - All Available Eyes)

	0-12M		12-24M		24-36M		0-36M	
	P1D	**MS**	**P1D**	**MS**	**P1D**	**MS**	**P1D**	**MS**
All Eyes								
N	120	116	118	108	112	102	112	104
Mean (D)	-0.58	-0.18	-0.33	-0.19	-0.30	-0.17	-1.24	-0.51
Difference (D)	+0.40		+0.15		+0.13		+0.73	
% Control	69%		44%		44%		59%	
8 years old at enrollment								
N	20	8	20	8	20	8	20	8
Mean (D)	-0.70	-0.38	-0.30	-0.17	-0.39	-0.21	-1.39	-0.76
Difference (D)	+0.32		+0.14		+0.18		+0.64	
9 years old at enrollment								
N	28	34	28	30	28	28	28	30
Mean (D)	-0.77	-0.26	-0.25	-0.25	-0.29	-0.23	-1.44	-0.72
Difference (D)	+0.51		-0.00		+0.06		+0.71	
10 years old at enrollment								
N	14	24	14	22	14	22	14	22
Mean (D)	-0.57	-0.13	-0.23	-0.17	-0.32	-0.13	-1.12	-0.39
Difference (D)	+0.44		+0.07		+0.19		+0.73	
11 years old at enrollment								
N	30	26	28	24	26	24	26	24
Mean (D)	-0.51	-0.18	-0.45	-0.21	-0.26	-0.09	-1.20	-0.47
Difference (D)	+0.33		+0.24		+0.17		+0.73	
12 years old at enrollment								
N	28	24	28	24	24	20	24	20
Mean (D)	-0.40	-0.06	-0.38	-0.11	-0.25	-0.18	-0.98	-0.28
Difference (D)	+0.35		+0.27		+0.06		+0.71	

% Control=Difference/P1D Mean (D) X 100

The year-to-year change in axial length showed pattern of progression similar to that of the refractive error progression. The following table shows the unadjusted mean change for all eyes with data within the interval.

Table 14: Year-to-Year Axial Length Change
(Unadjusted Mean - All Available Eyes)

	0-12M		12-24M		24-36M		0-36M	
	P1D	**MS**	**P1D**	**MS**	**P1D**	**MS**	**P1D**	**MS**
All Eyes								
N	120	116	118	108	112	102	112	104
Mean (mm)	+0.24	+0.09	+0.21	+0.12	+0.17	+0.11	+0.62	+0.30
Difference (mm)	-0.15		-0.10		-0.06		-0.32	
% Control	63%		46%		34%		52%	

% Control=Difference/P1D Mean (mm) X 100

Contact Lens Visual Acuity

At the dispensing visit, mean distance visual acuity (VA) with contact lenses was within one-letter for the two groups. Mean distance VA with contact lenses was similar in the two arms at all visits. (The table below, shows results for annual visits.) With over-refraction, distance VA remained similar for the two lens types and within one letter at each visit.

Table 15: Visual Acuity with Contact Lenses (logMAR)

	Control				MiSight			
	Dispensing	**12 months**	**24 months**	**36 Months**	**Dispensing**	**12 months**	**24 months**	**36 Months**
N (eyes)	148	120	120	112	140	116	110	104
Mean	-0.05	+0.01	+0.00	+0.00	-0.03	-0.04	-0.04	-0.01
SD	0.07	0.13	0.13	0.10	0.06	0.09	0.10	0.11

SD – standard deviation

Wearing Time

The mean wearing times during weekdays was 12 hours or more per day for both groups at each time-point. The mean wearing times during weekends were slightly lower than the weekday values, however, in each case, these were within half an hour of 12 hours/day. At each of the follow-up visits, the mean wearing times were greater than 6 days/week.

Table 16: Wearing Time Summary (All Available Subjects)

	Control				MiSight			
	One Week	**12 months**	**24 months**	**36 Months**	**One Week**	**12 months**	**24 months**	**36 Months**
N (subjects)	68	68	60	56	64	58	55	52
Wearing Time (hrs/day)	12.0	12.9	13.2	13.3	11.8	12.6	13.1	13.4
SD	2.1	1.3	1.5	1.5	2.3	1.8	1.3	2.3
Wearing Time (Days/Wk)	6.6	6.6	6.5	6.7	6.4	6.5	6.5	6.6
SD	0.8	0.5	0.5	0.5	1.2	0.6	0.5	0.5

SD – standard deviation

3. Subgroup Analyses

There was no significant interaction between lens type and site, age, sex or baseline refractive error. However, the sample size may have been insufficient to detect clinically significant effects.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

2. Retrospective Study of the Risk of Microbial Keratitis of Contact Lens Wear in Children (in marketed, non-MiSight, daily wear soft lenses)

The applicant performed a retrospective data audit (CV-18-01: Retrospective Cohort Study of Safety of Pediatric Soft Contact Lens Wear (ReCSS)) to estimate a rate of microbial keratitis and other adverse events in conventional, daily wear, soft contact lenses in children initially fit between the ages of 8-12 years of age. Microbial keratitis, although an uncommon event, is the most common vision-threatening adverse event associated with contact lens wear. To estimate this risk requires a sample size of thousands of patient-years. The risk has been examined in epidemiologic studies in the adult population, but has not been studied in children, because of the much lower level of contact lens use in children. The applicant provided real world evidence to roughly estimate the risk in children in the U.S. wearing marketed contact lenses. The primary statistical analysis was to calculate the incidence of microbial keratitis (cases per 10,000 patient-years) and a 2-sided 95% confidence interval, and to evaluate whether the upper confidence limit is less than 40 cases per 10,000 patient-years (0.4%).

Data were obtained by a medical record audit of children fitted with commercial soft contact lens in seven U.S. eye care practices. The lenses were commercially available soft contact lenses. MiSight lenses were not included in this audit as they were not yet available in the U.S.

Clinical records from 782 children fit in eye care practices and followed for an average of 2.7 years-of-wear were collected and evaluated. In total, this represents 2,134 patient-years of observation of children wearing soft contact lenses. Current status (last visit within 9 months) was obtained for 93% (728/782) of the patients. The age distribution of the cohort studied is shown below.

Table 17:Study Cohort

Age @ Fit	Subjects n (%)
8 years	54 (7%)
9 years	107 (14%)
10 years	162 (21%)
11 years	220 (28%)
12 years	239 (30%)
Total	782 (100%)

% = n/N(100); N = 782

Redacted clinical records were reviewed by an independent expert adjudication committee and a consensus diagnosis was determined for each case. Two cases were adjudicated as microbial keratitis from the eye care practices. Both cases resolved with 20/20 vision and the patients returned to contact lens wear. A mild scar remained in one case.

Based upon this data, the annualized rate of microbial keratitis is estimated at 2/2134 patient-years (0.094%) or 9.4/10,000 patient-years (95% C.I.: 2.3 to 37.7/10,000).

Table 18: Estimated Annual Incidence of Microbial Keratitis in Soft Contact Lenses (Total Patient-Years of Observation = 2134)

Adverse Events	Number of Cases	Annualized Rate/10,000	2-sided 95%CI
Microbial Keratitis	2	9.4	2.3 to 37.7

The rate of non-infectious infiltrative adverse events is summarized in the following table. Fourteen (14) non-infectious infiltrates were observed, four (4) of which were adjudicated as peripheral ulcers.

Table 19: Estimated Annual Incidence of Non-infectious Infiltrative Events (Total Patient-Years of Observation = 2134)

Adverse Events	Number of Cases	Annualized Rate	2-sided 95%CI
All Non-infectious Infiltrative Events	14	0.66%	0.36 - 1.10%
Peripheral Ulcer	*4*	*0.19%*	*0.05 - 0.50%*

This real world evidence study demonstrated that the upper confidence limit for incidence of microbial keratitis was less than 40 cases per 10,000 patient years.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. Each pivotal clinical study included four investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Device Panel (ODP), an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

A pivotal, multi-center, randomized, controlled, double-masked clinical study evaluated the effects of wear of the MiSight soft contact lens on the progression of myopia in children ages 8 – 12 (at baseline), compared to wear of a similar conventional soft contact lens. The change in myopia was evaluated based upon measurements of both:

- Cycloplegic autorefraction spherical equivalent refractive error; and
- Ocular axial length (using optical biometry).

Study results indicate that on both of these co-primary endpoints, the difference between the two arms showed smaller increases in myopia in the MiSight arm than the control arm that were statistically significant ($p < 0.0001$). Wear of the MiSight lens was effective in slowing the progression of myopia, compared to wear of a conventional contact lens, over the period studied. Over the 3-year study:

- The MiSight arm had a lower increase in mean cycloplegic, autorefractor-measured, myopia (SERE) than the control by 0.67 D (95% CI: 0.49 to 0.84 D).
- The MiSight arm had a lower increase in mean axial length than the control by 0.28 mm (95% CI: 0.20 to 0.36 mm).

These key effectiveness outcomes are based upon objective measurements, which generally are less subject to any potential bias in a study.

In addition, the MiSight lens was found to be effective in optically correcting the myopic refractive error in patients; contact lens visual acuity was similar in the two arms.

The study did not meet the protocol-specified criterion for "clinical significance" in the refractive endpoint, because the entire confidence interval on the difference between arms, in mean SERE, was not > 0.75 D. The difference between the study's refractive treatment effect of 0.67 D and this 0.75 D is 0.08 D.

It was noted that most of the difference between the arms occurred during the first year of treatment. It is not clear what the longer term benefits may be.

In addition, the study population had a higher proportion of Asian patients than the general U.S. population, but it is uncertain how much larger this may be than in the population of U.S. myopes. It is possible that the treatment effect may vary by race/ethnicity. To verify the treatment effect, one of the conditions of approval will be to re-evaluate effectiveness in a postapproval study in the U.S. pediatric population.

B. Safety Conclusions

The risks of the device are based on the nonclinical studies (extraction, compatibility, physicochemical properties and toxicology) as well as data collected in clinical studies conducted to support PMA approval as described above. It is noted that the MiSight lens is made of the same material as the Proclear daily disposable lens, which has been on the U.S. market for a number of years; and the lens parameters are similar except for the optical design.

In the pivotal, randomized, MiSight clinical study, there were no serious adverse events. There were 4 mild cases of asymptomatic, infiltrative keratitis, 3 of these were in two subjects in the control group. Out of the 130 eyes in the MiSight arm, 0.8% (1 eye) had infiltrative keratitis, 1.5% (2 eyes) had conjunctivitis, 3.1% (4 eyes) had blepharitis or meibomianitis, 2.3% (3 eyes) had tarsal hyperemia/lid irritation, 2.3% (3 eyes) had superficial punctate keratitis, and 0.8% (1 eye for each) had cases of foreign body, subconjunctival hemorrhage, and mild pannus. There were only two 2 cases of temporary reduction in best-corrected visual acuity of ≥ 2 lines, measured at one visit only. These were not related to any observation of significant eye problems and resolved without treatment. There were very few biomicroscopy findings greater than grade 2.

Due to the optical characteristics of the MiSight correction (which simultaneously provides an "in-focus" and an "out-of-focus" image), some wearers may notice reduced contrast, increased halos or glare around bright lights at night while wearing the lenses. Ghost images (double image) may also be noted.

Microbial keratitis is the most common cause of vision loss due to contact lens wear. The rate of microbial keratitis in children has not been studied, and the pivotal study was too small to assess this rate. Therefore, a "real world evidence," retrospective study of children, ages 8 – 12, wearing daily wear soft lenses in the U.S., was performed to get an estimate of rate of microbial keratitis. (None of these patients were wearing MiSight lenses, because it is not on the market in the U.S.) It found two cases in 2,123 patient-years of lens wear. This is a rate of 9.4/10,000 patient-years (95% C.I.:2.3 to 37.7/10,000). FDA notes that the results of the study provided a wide confidence interval for the estimate of the microbial keratitis incidence. This only provides evidence that the incidence of microbial keratitis in young children in daily wear is unlikely to be an extremely high rate. However, due to the large sample size necessary to study this event, it is extremely difficult to get a more precise estimate in a pre-approval study. Therefore, a much larger post-approval study to better estimate the incidence of microbial keratitis in MiSight lenses will be required as a condition of approval of this PMA.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The pivotal clinical study provides evidence that treatment with the MiSight lens is effective in slowing the progression of myopia by approximately 0.67 D over a 3-year period. During these three years, only 4% (4/112) of control patients progressed in myopia by the clinically insignificant amount of ≤ 0.25 D, while 41% (43/104) of MiSight patients showed a similar insignificant increase. Axial length increase was slowed by approximately 0.28 mm over 3-years. In addition, the device provides the benefits of optically correcting myopic refractive error; in the pivotal study, the contact lens corrected distance acuity in the MiSight arm was similar to that seen in the monofocal control arm.

The probable risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above. There were no serious adverse events seen in the MiSight pivotal clinical study, no cases of microbial keratitis observed, and the MiSight arm had only one case of non-infectious, asymptomatic infiltrative keratitis. The single use, daily disposable mode of wear that is used for the MiSight lens, minimizes the need for patient care and handling. The rate of microbial keratitis has not been studied, yet, in children wearing MiSight lenses, but the retrospective study of 8 – 12 year old wearers of other daily wear soft lenses estimated the rate to be approximately 9.4 cases per 10,000 patient-year.

Additional factors to be considered in determining probable risks and benefits for the MiSight daily disposable device included:

- There is no FDA-approved treatment to slow the progression of myopia at this time. Thus, the MiSight daily disposable contact lens represents novel technology.

- Although there are some limitations of this study, there are a large number of patients who can potentially benefit from a treatment to slow myopic progression. The probable benefits of the device are based on reliable, objective outcomes, collected in the pivotal clinical study.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the correction of myopic ametropia and slowing the progression of myopia in children with non-diseased eyes aged 8-12 years, with refraction of -0.75 D to -4.00 D spherical equivalent and ≤ 0.75 D of astigmatism at the initiation of treatment, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this PMA application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Myopic patients ages 8 – 12 at the initiation of treatment, when wearing the MiSight lenses can expect to get optical correction of the myopia, yielding good distance acuity, and can expect, after three years, to have nearly 0.75 D lower myopic error than if they had worn a conventional soft contact lens. Risks associated with MiSight lens wear, appear to be similar to those associated with the wear of other marketed daily disposable soft contact lenses.

XIII. CDRH DECISION

CDRH issued an approval order on November 15, 2019. The final conditions of approval cited in the approval order are described below.

1. MiSight 1 Day Post-Approval Study for Effectiveness and Visual Symptoms (PAS001)

You are required to provide post-approval effectiveness data to FDA on the *MiSight 1 Day* Contact Lens. You agreed to a study outline on November 1, 2019. *MiSight* 1 Day Effectiveness Post-Approval Study is designed to:

- confirm in the U.S. population that there are clinically meaningful differences (super-superiority margin of 0.50D) in the mean change of cycloplegic refractive error and axial length change from baseline after three years of using *MiSight* 1 Day lenses among intended patient population compared to the mean changes in a control group using conventional daily disposable lenses;

- estimate the effects of race, baseline cycloplegic spherical equivalent refractive error, and baseline age on the treatment effect;

- assess the effects of the *MiSight* 1 Day on the patients' visual symptoms and the effects on patient activities of daily living, using an appropriately validated PRO measure; and adding specific endpoints and analyses to the study protocol to evaluate the rates of the more important symptoms; and

- assess the stability of the myopia reduction over 1-year post-treatment among those who completed the 3-year confirmation study follow-up.

The study population will consist of:
children ages of 8-12, who have best corrected visual acuity of at least 20/25 bilaterally, with refractive error within the approved power range of *MiSight* 1 Day lenses (-0.75 D to – 4.00D spherical equivalent and ≤ 0.75 D of astigmatism at the initiation of treatment), who are free of ocular disease or abnormalities (including any corneal scar), and who are not under medication that would interfere with contact lens wear, or are using or have used any pharmaceuticals or other methods for control of myopia will be identified for inclusion in the study. (Full statement in the protocol will exclude all patients who have any of the specific Contraindications in labeling.)
The study is intended to assess the effectiveness of the approval device in three phases.

Phase A: PRO
Develop new or modify existing PRO measures, and validate, using appropriate qualitative methods to ensure content coverage and understanding of the relevant concepts by patients and their parents.

Provide any necessary changes to the existing study protocol to incorporate this validation and modification of the PRO measure.

Phase B: US Study for Effectiveness and Visual Symptoms
A multicenter, double-blind, randomized prospective clinical trial will be conducted to confirm that there are clinically meaningful differences in the mean change of cycloplegic refractive error (super-superiority margin of 0.50D) and mean axial length change (super-superiority margin of 0.2 mm) from baseline after three years of using *MiSight* 1 Day lenses among intended patient population compared to the mean changes in a control group using conventional daily disposable lenses, adjusting for the effect of age, degree of initial myopia and the interaction effect between age and degree of initial myopia. Phase B will also assess the adverse visual effects of the *MiSight* 1 Day, as noted above.

This study will enroll a minimum of 675 patients in the *MiSight* 1 Day treatment group and 225 in the control group from all eligible patients in 25-35 US clinical sites and will have a minimum of 664 total number of evaluable patients (498 patients in the treatment group and 166 patients in the control group) completing 3 years of wear.

Phase C: Cessation Study
To assess the stability of the myopia reduction over 1-year post-treatment, all of those who completed the 3-year confirmation study follow-up will be continuously followed

into a fourth year. A minimum number of 598 evaluable patients (with 448 in the treatment group and 150 in the control group) will complete this phase of the study (assuming a 10% attrition rate in the 4th year).

2. MiSight 1 Day Safety Post-Approval Study (PAS002)

You are required to provide post-approval safety data to FDA on the *MiSight 1 Day* Contact Lens. You agreed to a study outline on November 1, 2019. This study is designed to confirm that the incidence of Microbial Keratitis (MK) is lower than 0.002/patient-year among the intended patient population in the US.

This will be a cohort study nested within integrated health care and coverage organization systems or integrated (optometry/ophthalmology) eyecare practices. Consecutive subjects receiving the MiSight lens, who meet the inclusion criteria, will be prospectively identified to be included in the study, and will be consented for the use and release of their health care encounter data to be used for this safety study. Subsequent occurrence of the outcomes of interest will be identified using electronic health records and claims data within the integrated health care and coverage organization(s) or integrated optometry/ophthalmology practices. Additionally, safety data from the *MiSight 1 Day Post-Approval Study for Effectiveness and Visual Symptoms* will be used to supplement this safety study.

The study population will consist of children ages 8-12, who are prescribed the MiSight lens for both eyes, who have best corrected visual acuity of at least 20/25 bilaterally, with refractive error within the approved power range of MiSight lenses (-0.75D to -4.00D spherical equivalent and ≤ 0.75D of astigmatism at the initiation of treatment), who are free of ocular disease or abnormities (including any corneal scar), and who are not under medication that would interfere with contact lens wear or any pharmaceuticals for control of myopia will be identified for inclusion in the study. (Children who have any of the specific contraindications in the labeling will not be included in the study.) Children that are being fitted for the MiSight and who will first start using the device at the time of study initiation or thereafter will be included in the analysis.

Data will be captured on the following endpoints: microbial keratitis, the incidence of loss of best-corrected visual, the incidence of non-infectious infiltrative keratitis, and peripheral non-infectious ulcers. Safety data will be captured for all subjects through three years post first-fitting. A minimum follow-up of 8 months is required for each subject. All cases of MK among the enrollees will be identified and reported to the FDA.

Incidence rates per patient-year will be estimated with 95% confidence intervals for each endpoint listed above.

To estimate the microbial keratitis rate, accrual of 8,500 patient-years is needed. A minimum of 6,000 patient-years, from 2,000 prospectively identified subjects will be accumulated from the safety PAS, and a minimum of 2,500 patient-years will be accumulated from the subjects enrolled in the e*ffectiveness PAS*.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

Kleinstein RN, et al. Refractive Error and Ethnicity in Children. Arch Ophthalmol (121), Aug 2003, 1141-1147.