July 18, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Single-use colored vision corrective contact lens
Brand Name	MiSight 1 Day
Applicant	CooperVision Japan, Inc.
Date of Application	August 22, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on July 18, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with no designation as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The product should be approved with the following approval condition.

Approval Condition

1. The applicant is required to take necessary measures to ensure that the product is used appropriately only in eligible patients under the supervision of physicians with adequate knowledge and experience.

Review Report

June 26, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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Reviewing Office	Office of Medical Devices I

Review Results

June 26, 2025

Classification	Instrument & Apparatus 72, Lens for Vision Correction
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Results of Review

MiSight 1 Day (hereinafter referred to as MiSight) contact lens is a daily disposable soft contact lens and indicated for vision correction and slowing the progression of myopia.

The applicant submitted non-clinical data that support the performance of MiSight. There was no particular problem in the data submitted.

The applicant submitted clinical data of MiSight from the MIST401 (Part 1) and MIST402 studies conducted in Portugal, the UK, Singapore, and Canada, and the MIST-J study conducted in Japan. The applicant also submitted data from results of the MIST401 (Part 2) study as reference data.

The MIST401 (Part 1) study is a randomized, double-masked, parallel-group study to evaluate the efficacy and safety of MiSight versus an approved product, Proclear 1 Day, in patients aged 8 to 12 years with low-to-moderate myopia. The primary endpoints were defined as “change from baseline to 3 years in cycloplegic autorefraction spherical equivalent” and “change from baseline to 3 years in axial length.” MiSight demonstrated superiority over the control for both endpoints. The between-group differences [95% confidence interval (CI)] for the first and second primary endpoints were 0.67 D [0.49, 0.84] and −0.28 mm [−0.36, −0.20], respectively (based on the linear mixed model analysis; $P < 0.0001$). There was no clear difference in the safety profile between the MiSight and control groups. Patients who completed the MIST401 (Part 1) study were enrolled in the MIST401 (Part 2) study for long-term assessment. The results of the MIST401 (Part) showed that the long-term wear of MiSight raised no safety concerns. Patients who completed the MIST401 (Part 2) study were enrolled in the MIST402 study which assessed myopia progression after discontinuation of lens wear. Results suggested that myopia progression after the lens wear discontinuation was unlikely to be a clinical issue. The MIST-J study was conducted to confirm the extrapolability of foreign clinical study data to the Japanese population, and it yielded results consistent with those of the MIST401 (Part 1) study. Therefore, PMDA has concluded that the foreign clinical study data can be extrapolated to Japanese data.

Since MiSight is a medical device to slow myopia progression and mainly intended for use in children, it should be used under the appropriate supervision and management by a physician. In addition, periodic examinations should be performed to monitor myopia progression and the occurrence of complications, and the risk-benefit balance of MiSight should be assessed before use. Based on the above, PMDA has concluded that necessary measures should be taken so that MiSight is sold exclusively to patients who are confirmed to use the device under the appropriate supervision and management by a physician.

As a result of its review, PMDA has concluded that MiSight may be approved for the intended use shown below, with the following approval condition, and that the present application should be deliberated by the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Vision correction and slowing the progression of myopia

Approval Condition

The applicant is required to take necessary measures to ensure that the product is used appropriately only in eligible patients under the supervision of physicians with adequate knowledge and experience.

Review Report

June 26, 2025

Product for Review

Classification	Instrument & Apparatus 72, Lens for Vision Correction
Term Name	Single-use colored vision corrective contact lens
Brand Name	MiSight 1 Day
Applicant	CooperVision Japan, Inc.
Date of Application	August 22, 2024
Proposed Intended Use	Vision correction and slowing the progression of myopia in patients aged ≥8 years with myopic ametropia potentially leading to axial elongation

Table of Contents

List of Abbreviations

CI	confidence interval
GCP	good clinical practice

I. Product Overview

MiSight 1 Day (hereinafter referred to as MiSight) is a daily disposable soft contact lens and is intended for myopia correction and slowing the progression of myopia.

MiSight employs a concentric bifocal lens design which consists of myopia correction zones that correct myopia and treatment zones that create myopic defocus, thereby reducing axial elongation and slowing myopia progression (Figure 1). The material used in the MiSight lens is the same as that of the applicant's approved product "Proclear 1 Day" (Approval number, 22000BZX01462000).

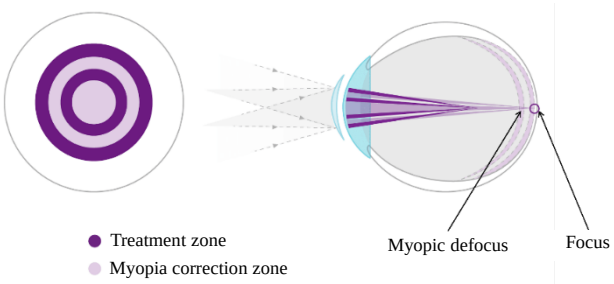

Figure 1. Product overview

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in support of the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on MiSight declared that they did not fall under Chapter 3, Item 5 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Myopia is defined as a refractive error of the eye where parallel light rays entering the eye without any accommodation focus in front of the retina rather than on it or light rays emitted from a point at a finite distance in front of the eye converge at a point in front of the retina. Myopia with autorefraction spherical equivalent (spherical power + cylindrical power ×1/2) of ≥−0.5 D and <−3.0 D, ≥−3.0 D and <−6.0 D, and ≥−6.0 D are classified as low, moderate, and high myopia, respectively.[1] Myopia typically develops at the ages of approximately 6 to 8 years and progresses through the age of 15 or 16 years.[2] In Japan, the population with myopic eyes has been increasing with lifestyle changes, such as decreased time outdoors and increased near-work activities.[3] Since high myopia is considered a risk factor of severe complications associated with visual impairment, such as retinal detachment, myopic maculopathy, and glaucoma,[4] slowing the progression of myopia is expected to prevent reduced quality of life and severe ocular complications associated with visual impairment. In Japan, a drug product "Ryjusea Mini Ophthalmic Solution 0.025%" (Approval number, 30600AMX00287) was approved for slowing the progression of myopia in December 2024. However, there is no medical device with similar indications.

The refractive state of the eye is determined by the corneal power, crystalline lens power, and axial length, and myopia progression is thought to be highly affected by the axial elongation.[5] Although the precise mechanism of elongation of axial length remains unknown, hypermetropic defocus where light rays entering the eye focus outside of the retina is considered to enhance remodeling of sclera and thereby extend axial length.[6] MiSight has myopia correction zones to correct myopia and treatment zones to create myopic defocus. These zones are concentrically placed in the lens. The myopia correction zones serve to correct visual acuity, and the treatment zones to create myopic defocus, thereby slowing the progression of myopia.

For the development of MiSight indicated for slowing the progression of myopia, clinical studies were initiated overseas in November 20[redacted]. In Japan, clinical studies were initiated in [redacted] 20[redacted]. Based on the data from Japanese and foreign clinical studies that demonstrated the efficacy of MiSight in slowing the progression of myopia and its safety, the applicant has submitted an application for marketing approval.

1.A.(2) Use in foreign countries

Table 1 shows the approval status of MiSight in major foreign countries.

Table 1. Marketing approval status of MiSight in major foreign countries

Country and region	Intended use	Approval date	Shipment quantity*
European Union	Slowing the progression of myopia and correction of ametropia in children (aged 6-18 years)	August 2009	[redacted] lenses
Hong Kong	MiSight corrects ametropia and may slow the progression of myopia in children (aged 6-18 years). In a clinical study, the progression of myopia was reduced by ≥30% in 75% of children aged 11 to 14 years who wore the lenses for 12 hours (8-16 hours) a day and 6.4 days (5-7 days) a week. MiSight may relieve symptoms resulting from a feeling of dryness during the lens wear associated with mild discomfort with lens wear and evaporation or lack of aqueous tear in the lacrimal fluid (except Sjogren's syndrome). Single-use daily disposable lens.	August 2012	[redacted] lenses
Singapore	MiSight corrects myopia and slows the progression of myopia. It is intended for use in children with non-diseased eyes who at the initiation of treatment are 8 to 12 years of age and have a refraction of −0.75 D to −4.00 D (spherical equivalent) with ≤−0.75 D of astigmatism. The lens is to be discarded after each removal.	January 2013	[redacted] lenses
US	MiSight corrects myopia and slows the progression of myopia. It is intended for use in children with non-diseased eyes who at the initiation of treatment are 8 to 12 years of age and have a refraction of −0.75 D to −4.00 D (spherical equivalent) with ≤−0.75 D of astigmatism.	November 2019	[redacted] lenses
Taiwan	MiSight corrects myopia of −0.25 to −6.00 D and slows the progression of myopia in children aged 8 to 15 years. It is intended for use in non-aphakic children with non-diseased eyes. The lens is to be discarded after each removal. It is prescribed only to patients who were examined by an ophthalmologist and diagnosed as being eligible for use. Patients are required to undergo periodic examinations according to the schedule specified by the ophthalmologist.	January 2020	[redacted] lenses
South Korea	MiSight corrects myopia and slows myopia progression. It is intended for use in children with non-diseased eyes who at the initiation of treatment are 8 to 12 years of age and have a refraction of −0.75 D to −4.00 D (spherical equivalent) with ≤−0.75 D of astigmatism.	November 2020	[redacted] lenses
China	MiSight is intended for the correction of myopia in non-aphakic children with non-diseased eyes who at the initiation of treatment are 8 to 12 years of age and have a refraction of −0.75 D to −4.00 D (spherical equivalent) with ≤−0.75 D of astigmatism. It has a concentric bifocal lens design and creates myopic defocus due to light rays that are partially focused in front of the retina, thereby slowing axial elongation. MiSight must be prescribed by an ophthalmologist of intermediate or higher level at a medical institution and followed by continued examinations. The lenses must be used strictly in accordance with the instructions for use.	August 2021	[redacted] lenses

* January 2017 to December 2023

1.A.(3) Occurrence of malfunctions and adverse events in foreign countries

Table 2 shows the occurrence of malfunctions of MiSight and adverse events in foreign countries that were reported to the regulatory authorities as of April 30, 2025.

Table 2. Occurrence of malfunctions of MiSight and adverse events in foreign countries

Event	Number of events
Corneal ulcer	5
Keratitis	2
Infective keratitis	2
Acanthamoeba keratitis	2
Anaphylactic shock	2
Eye infection bacterial	1
Uveitis	1
Iritis	1
Corneal epithelium disorder	1
Acquired internal strabismus	1
Herpes zoster	1

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

Performance and safety specifications for MiSight were established based on the "Criteria for Vision Corrective Contact Lens" (Public Notice of the Ministry of Health, Labour and Welfare [MHLW] No. 349 dated October 5, 2001) and Attachment 2 "Technical standards for soft (hydrogel) contact lens" of the "Revision of the Approval Criteria for Contact Lens (Part 2) (in Japanese)" (PSEHB Notification No. 0411-8 dated April 11, 2019). The applicant submitted data explaining the validity of each specification.

2.(1).B Outline of the review conducted by PMDA

PMDA instructed the applicant to establish specifications for the treatment zones of MiSight in addition to those proposed by the applicant.

The applicant selected the [redacted] power test as a specification to demonstrate that the treatment zones of MiSight have [redacted] refractive power of 2.00 D.

PMDA reviewed the added specifications including that explained in Section "2.(6) Tests to support device performance" described later. As a result, PMDA has concluded that there is no particular problem with the added specifications.

2.(2) Physical and chemical properties

2.(2).A Summary of the data submitted

The raw material of MiSight were the same as that of the approved product "Proclear 1 Day." The applicant omitted the submission of data on the physical and chemical properties.

2.(2).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of data on the physical and chemical properties.

2.(3) Biological safety

2.(3).A Summary of the data submitted

The raw materials, manufacturing process steps, and manufacturing process of MiSight were the same as those of the approved product "Proclear 1 Day." The applicant omitted the submission of data on biological safety.

2.(3).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of data on biological safety.

2.(4) Mechanical safety

2.(4).A Summary of the data submitted

The raw materials of MiSight were the same as those of the approved product "Proclear 1 Day." The applicant omitted the submission of data on the mechanical safety (strength).

2.(4).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of data on the mechanical safety.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

The raw materials, packaging, and sterilization method of MiSight were the same as those of the approved product "Proclear 1 Day." The applicant omitted the submission of data on the safety and durability.

2.(5).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with the omission of data on the safety and durability.

2.(6) Tests to support device performance

2.(6).A Summary of the data submitted

To support the performance of MiSight, the applicant submitted data from the studies evaluating the shape and appearance, diameter, thickness, base curve, and vertex power based on Attachment 2 "Technical standards for soft (hydrogel) contact lens" of "Revision of the Approval Criteria for Contact Lens (Part 2)" (in Japanese) (PSEHB Notification No. 0411-8 dated April 11, 2019). The applicant also submitted data from the following studies: [redacted] power test using a lensmeter to evaluate whether the intended power relative to vertex power was located in the treatment zones; and a test using [redacted] to evaluate whether the intended power was located in the myopia correction zones and the treatment zones.

2.(6).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the mechanism of action of MiSight to slow the progression of myopia and the rationale for selecting [redacted] power of 2.00 D in the treatment zones.

The applicant's explanation:
A study in which lenses were worn in chicks and rhesus monkeys reported that axial length was increased by hypermetropic defocus created by lenses with negative powers while axial elongation was reduced by myopic defocus generated by lenses with positive powers.[7,8,9]

In a study in children who wore monovision glasses, the dominant and non-dominant eyes of children were fully corrected and under-corrected, respectively, with a maximum difference of 2.00 D. The study reported that monovision wear was associated with slower progression of myopia in the non-dominant eye compared with the dominant eye. The result suggested that axial elongation was reduced by myopic defocus resulting from under-correction in the non-dominant eye.[10]

Based on the above findings, MiSight was designed to concentrically place optical zones with a power to correct myopia and with a power of 2.00 D in order to correct myopia and create myopic defocus. A study in humans reported that myopic defocus was generated by the MiSight lens wear.[11]

PMDA's view:
Based on the reports that the progression of myopia was mainly attributable to axial elongation, myopic defocus contributed to suppression of axial elongation in multiple animal studies and published literature, and MiSight produced myopic defocus, MiSight is expected to slow the progression of myopia.

In conclusion, PMDA reviewed the data on performance and concluded that there was no particular problem.

2.(7) Tests to support method of use of the device

2.(7).A Summary of the data submitted

The method of use of MiSight were the same as that of the approved product "Proclear 1 Day," which is intended for vision correction only. The applicant omitted the submission of data supporting the method of use of MiSight. The age at the start of lens wear differs from that for contact lenses commonly marketed, and MiSight is mainly intended for use in children. Therefore, the data submitted were evaluated to confirm that MiSight is suitable for use in eligible patients as described in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

2.(7).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of data supporting the method of use of the device and decided to make a conclusion on this issue, based on the evaluation results in Section "6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare."

2.(8) Usability engineering

2.(8).A Summary of the data submitted

For the usability engineering process of MiSight, the applicant submitted data demonstrating its conformity to BS EN 62366-1:2015+A1:2020 "Medical devices - Application of usability engineering to medical devices."

2.(8).B Outline of the review conducted by PMDA

PMDA reviewed the data on the conformity to BS EN 62366-1:2015+A1:2020 "Medical devices - Application of usability engineering to medical devices" and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that MiSight meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (Public Notice of MHLW No. 122 of 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of MiSight to the Essential Principles.

(1) PMDA's view on the conformity of MiSight to Article 1, which stipulates prerequisites, etc. for designing medical devices (particularly requirements for users, such as expected levels of technical knowledge and experience, and the expected level of education and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA," considerations for appropriate selection of eligible patients are important in MiSight, and PMDA decided to impose an approval condition so that the applicant will take measures for preventing the selection of ineligible patients.

(2) PMDA's view on the conformity of MiSight to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," the submitted clinical data confirmed that the use of MiSight resulted in corrected visual acuity and slowing the progression of myopia, and the selection of eligible patients enabled effective and safe use of MiSight. Therefore, MiSight conforms to Articles 3 and 6.

(3) PMDA's view on the conformity of MiSight to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on precautions, etc.):
As described later in Section "6.B Outline of the review conducted by PMDA," physicians should fully inform users of risks associated with MiSight before use and should select eligible patients. Therefore, the applicant is required to provide information to physicians through the Information on precautions, etc.

In conclusion, PMDA reviewed the conformity of MiSight to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with JIS T 14971 “Medical devices - Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the description presented in Section “3.B Outline of the review conducted by PMDA” and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the manufacturing process and manufacturing establishment as information on the manufacturing process of MiSight. For quality control, the applicant submitted data on inspection items performed during the process of manufacturing.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted clinical evaluation data from the following studies of MiSight: MIST401 (Part 1) and MIST402 studies conducted in 4 foreign countries and the MIST-J study that confirmed the extrapolability of foreign clinical study data to the Japanese population (attached document), and the MIST401 (Part 2) study (reference data). Table 3 shows a list of clinical studies.

Table 3. List of clinical studies

Location	Study	Study population	Primary objective	Positioning
Foreign	MIST401 (Part 1) study	Patients aged 8 to 12 years with low to moderate myopia	Efficacy and safety	Attached document
	MIST401 (Part 2) study	Patients who completed the MIST401 (Part 1) study	Long-term efficacy and safety	Reference data
	MIST402 study	Patients who completed the MIST401 (Part 2) study	Myopia progression after discontinuation	Attached document
Japan	MIST-J study	Patients aged 8 to 12 years with low to moderate myopia	Efficacy and safety	Attached document

6.A.(a) MIST401 (Part 1) study (NCT No. 01729208; study period, November 2012 to [redacted] 20[redacted])

A randomized, double-masked, parallel-group study was conducted in patients aged 8 to 12 years with low-to-moderate myopia at 4 study sites in foreign countries (Portugal, the UK, Singapore, and Canada) to evaluate the efficacy and safety of MiSight versus the approved product “Proclear 1 Day.” Table 4 shows the summary of the study.

Table 4. Summary of MIST401 (Part 1) study

Study	MIST401 (Part 1) study
Study design	Randomized, double-masked, parallel-group study
Inclusion criteria	(1) Subjects aged 8 to 12 years at the baseline examination (2) Subjects who have read an assent document, been given an explanation, understood its content, and signed the informed assent form (3) The parent or legal guardian of the subject has read a consent document, been given an explanation, understood its content, and signed the informed consent form. (4) Both the patient and his or her parent or legal guardian have understood the nature of the study and are willing to adhere to the instructions set forth in the protocol. (5) Both the patient and his or her parent or legal guardian have agreed to adhere to the examination schedule and are willing to adhere to the entire schedule set forth in the protocol during the study period. (6) Subjects who have agreed to accept treatment as assigned by the randomization (7) Subjects who have agreed 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 (8) Subjects who possess wearable and visually functional eyeglasses (9) Subjects who are in good general health based on the knowledge of their parent or legal guardian (10) Subjects who have best-corrected visual acuity by noncycloplegic manifest refraction of +0.10 logMAR (20/25 Snellen equivalent) or better in each eye (11) Subjects who meet the following refractive criteria determined by cycloplegic autorefraction at baseline: Spherical equivalent between −0.75 and −4.00 D, astigmatism ≤−0.75 D, and a refractive difference between the right and left eyes <1.00 D
Exclusion criteria	(1) Subjects who have previously worn, or currently wear contact lenses, including orthokeratology lenses (2) Subjects who appear to exhibit poor personal hygiene (3) Subjects who are currently participating in another clinical study, or participated within 30 days prior to the study (4) The subject's parent or legal guardian, or a close relative is a member of the study site staff, including the investigators. (5) Subjects who are currently using or previously used bifocals, progressive addition lenses, atropine, pirenzepine, or any other myopia control treatment (6) Subjects who were born earlier than 30 weeks or weighed less than 1500 g at birth (7) Subjects who regularly use ocular medications (prescription or over-the-counter), artificial tears, or wetting agents (8) Subjects who use 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 (e.g., pseudoephedrine, phenylephrine), antihistamines (e.g., chlorpheniramine, diphenhydramine), prednisolone, or Ritalin (methylphenidate). (9) Subjects with a known allergy to fluorescein, benoxinate, proparacaine, or tropicamide (10) Subjects with a history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, infective ocular inflammation, or other recurrent ocular inflammation (11) Subjects with strabismus by cover test at far (4 m) or near (40 cm) wearing distance correction (12) Subjects with known ocular or systemic illness, such as, but not limited to; anterior uveitis, iritis, episcleritis, scleritis, glaucoma, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, or diabetes mellitus. (13) Subjects with any ocular, systemic or neuro-developmental conditions that could influence refractive development. Such as, but not limited to; persistent pupillary membrane, vitreous haemorrhage, cataract, corneal scar, eyelid ptosis due to haemangioma, Marfan's syndrome, Down's syndrome, Ehlers-Danlos syndrome, Stickler's syndrome, ocular albinism, or retinopathy of prematurity. (14) Subjects with keratoconus or an irregular corneal shape (15) Subjects with biomicroscopic findings that would contraindicate contact lens wear including, but not limited to: a. Corneal scars within the visual axis b. Neovascularization or ghost vessel formation in ≥1.5 mm from the corneal limbus c. Any active anterior segment ocular illness that would contraindicate contact lens wear d. Giant papillary conjunctivitis of Grade ≥2 e. Allergic or seasonal conjunctivitis (if the study investigator believes it could significantly influence 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.

Target sample size	600 eyes of 300 patients (300 eyes of 150 patients in the MiSight group and 300 eyes of 150 patients in the control group) The required sample size was calculated to be 174 patients under the conditions of two-sided significance level of 5%, power of 90%, standard deviation of 0.50 D, and detection of therapeutic efficacy of 0.25 D/year. Assuming an annual dropout rate of 14%, the target sample size was determined to be 300 patients. However, the subject enrollment was completed before the planned sample size was achieved, because the enrollment was delayed from the initial plan and considering that 22 subjects were required to detect the therapeutic efficacy of 0.75 D for 3 years.
Directions for use	Daily wear, daily disposable The contact lenses are to be worn for a minimum of 10 hours and a maximum of 15 hours per day, at least 6 days per week. In the measurement of corrected visual acuity with contact lens (distant vision), any change of the lens power should be considered with reference to manifest refraction values if additional correction of ≥±0.50 D is required.
Follow-up period	3 years
Endpoints	***Efficacy*** Change from baseline to 3 years in cycloplegic autorefraction spherical equivalent (primary endpoint) Change from baseline to 3 years in axial length (primary endpoint) Corrected visual acuity with contact lens, etc. ***Safety*** Slit lamp microscopy findings, subjective symptoms related to visual disorders, adverse events, malfunctions, etc. ***Other*** Autorefraction spherical equivalent, etc. during fixation to each distance

Figure 2 shows patient disposition in the MIST401 (Part 1) study. The MIST401 (Part 1) study enrolled 187 patients, of which 144 patients were randomized. All of the randomized patients were included in the efficacy and safety analysis sets. The study was discontinued prematurely in 36 patients (18 in the MiSight group and 18 in the control group) and the common reasons for discontinuation were consent withdrawal in 8 patients (3 in the MiSight group and 5 in the control group) and poor fitting in 6 patients (3 in the MiSight group and 3 in the control group). Of the patients who discontinued the study, 9 patients (5 in the MiSight group and 4 in the control group) were randomized, but failed to receive lens prescription.

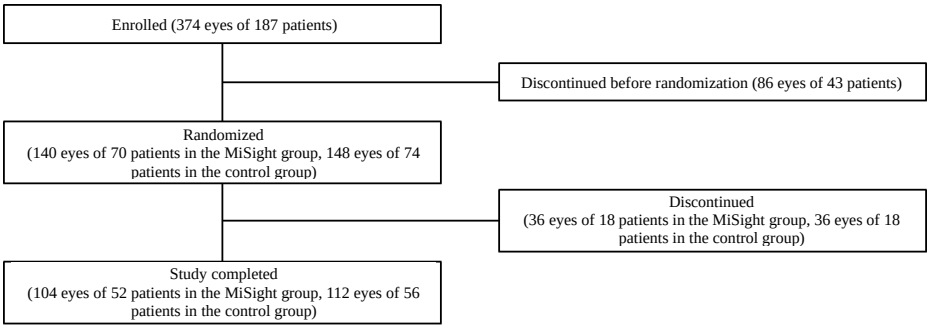

Figure 2. Patient disposition

6.A.(a).(1) Patient characteristics

There was no clear difference in the patient characteristics between the MiSight and control groups as shown in Table 5.

Table 5. Patient characteristics

Item		Control (148 eyes of 74 patients)	MiSight (140 eyes of 70 patients)
Sex	Male	50% (37 patients)	54% (38 patients)
	Female	50% (37 patients)	46% (32 patients)
Age (years)*		10.1 ± 1.4	10.1 ± 1.3
Cycloplegic spherical power (D)*		-2.00 ± 0.80	-1.83 ± 0.77
Cycloplegic cylinder power (D)*		-0.40 ± 0.21	-0.40 ± 0.21
Cycloplegic autorefraction spherical equivalent (D)*		-2.19 ± 0.81	-2.02 ± 0.77
Axial length (mm)*		24.42 ± 0.66	24.46 ± 0.70

* Mean ± standard deviation (SD)

6.A.(a).(2) Efficacy

6.A.(a).(2).1) Primary endpoint

Table 6 and Figure 3 show the results of the change from baseline in cycloplegic autorefraction spherical equivalent. Table 7 and Figure 4 show the change from baseline in axial length. The study results demonstrated the superiority of MiSight over the control. Multiplicity was controlled by the fixed sequence procedure in which cycloplegic autorefraction spherical equivalent and axial length were tested in this order. The results at 1 and 2 years were not used in the decision for the study continuation.

Table 6. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

Evaluation time point	Treatment group	Number of eyes	Autorefraction spherical equivalent	Change in autorefraction spherical equivalent *1,*2	Between-group difference [95% CI]*2	*P*-value*2,*3
Baseline	Control	148	-2.19 ± 0.81	-	-	-
	MiSight	140	-2.02 ± 0.77	-		
At 1 year	Control	120	-2.80 ± 1.01	-0.64 ± 0.07	0.38 [0.21, 0.55]	-
	MiSight	116	-2.17 ± 0.85	-0.27 ± 0.07		
At 2 years	Control	120	-3.13 ± 1.08	-0.99 ± 0.07	0.52 [0.35, 0.69]	-
	MiSight	110	-2.33 ± 0.92	-0.47 ± 0.07		
At 3 years	Control	112	-3.45 ± 1.14	-1.31 ± 0.08	0.67 [0.49, 0.84]	<0.0001
	MiSight	104	-2.52 ± 0.98	-0.65 ± 0.07		

Mean ± SD

*1 Least squares mean ± standard error (SE)

*2 Analysis based on a linear mixed model with treatment group, examination, study site, and all secondary interactions and tertiary interactions as fixed effects; age group, sex, ethnicity, and myopia (autorefraction spherical equivalent or axial length) of subjects at baseline as fixed covariates; and subjects (by study site) and eyes as a random effect.

*3 A two-sided significance level of 5%

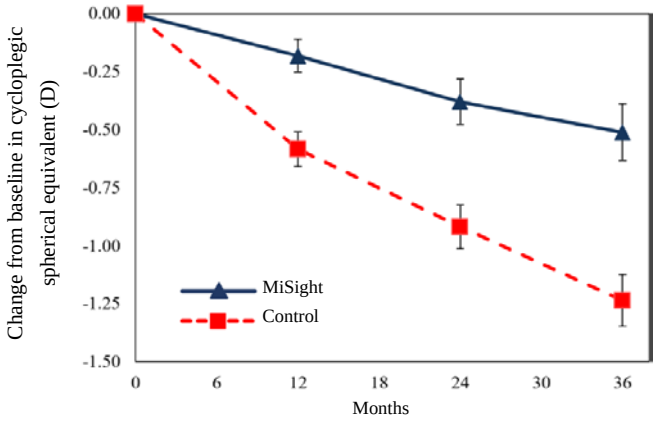

Figure 3. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

Table 7. Change in axial length from baseline (mm)

Evaluation time point	Treatment group	Number of eyes	Axial length	Change in axial length[*1,*2]	Between-group difference [95% CI][*2]	*P*-value[2,*3]
Baseline	Control	148	24.42 ± 0.66	-	-	-
	MiSight	140	24.46 ± 0.70	-		
At 1 year	Control	120	24.68 ± 0.66	0.23 ± 0.03	-0.13 [-0.21, -0.05]	-
	MiSight	116	24.52 ± 0.69	0.10 ± 0.03		
At 2 years	Control	120	24.88 ± 0.70	0.45 ± 0.03	-0.22 [-0.30, -0.14]	-
	MiSight	110	24.60 ± 0.64	0.23 ± 0.03		
At 3 years	Control	112	25.07 ± 0.74	0.62 ± 0.03	-0.28 [-0.36, -0.20]	<0.0001
	MiSight	104	24.76 ± 0.66	0.34 ± 0.03		

Mean ± SD
*1 Least squares mean ± SE
*2 Analysis based on a linear mixed model with treatment group, examination, study site, and all secondary interactions and tertiary interactions as fixed effects; age group, sex, ethnicity, and myopia (autorefraction spherical equivalent or axial length) of subjects at baseline as fixed covariates; and subjects (by study site) and eyes as a random effect.
*3 A two-sided significance level of 5%

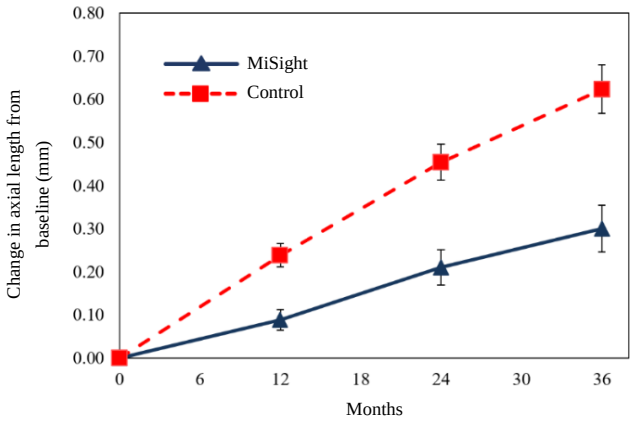

Figure 4. Change in axial length from baseline (mm)

6.A.(a).(2).2) Corrected visual acuity with contact lens

Table 8 shows corrected visual acuity with contact lens. Throughout the study period, mean distance visual acuity was ≤−0.01 logMAR (equivalent to decimal visual acuity of ≥1.02) in the MiSight group and ≤+0.01 logMAR (equivalent to decimal visual acuity of ≥0.98) in the control group. Mean near visual acuity was ≤−0.05 logMAR (equivalent to decimal visual acuity of ≥1.12) in the MiSight group and ≤−0.07 logMAR (equivalent to decimal visual acuity of ≥1.17) in the control group.

Table 8. Contact lens-corrected visual acuity (logMAR)

Evaluation time point	Treatment group	Number of eyes	Distance vision	Near vision
Baseline	Control	148	-0.05 ± 0.07	-0.07 ± 0.11
	MiSight	138[*]	-0.03 ± 0.06	-0.05 ± 0.10
At 1 year	Control	120	+0.01 ± 0.13	-0.11 ± 0.11
	MiSight	116	-0.04 ± 0.09	-0.09 ± 0.10
At 2 years	Control	120	0.00 ± 0.13	-0.11 ± 0.09
	MiSight	110	-0.04 ± 0.10	-0.11 ± 0.09
At 3 years	Control	112	0.00 ± 0.10	-0.10 ± 0.08
	MiSight	104	-0.01 ± 0.11	-0.09 ± 0.09

Mean ± SD
* Data was not collected in 1 subject due to improper lens fitting.

6.A.(a).(3) Safety

6.A.(a).(3).1) Slit lamp microscopy findings

Table 9 shows slit lamp microscopy findings of Grade >1. There was no trend towards an increase in number of events over time. As shown in Table 10, the incidences of events were 47.7% (61 of 128 patients) in the MiSight group and 30.1% (41 of 136 patients) in the control group. The incidence rates per 100 person-years adjusted according to the total wearing time were 35.8 in the MiSight group and 20.8 in the control group. In the MiSight group, 1 patient experienced Grade 3 palpebral conjunctival abnormality, and Grade 3 limbal hyperaemia and Grade 3 bulbar conjunctival hyperaemia occurred in the same patient. However, these events did not lead to study discontinuation, and the outcomes were reported as "resolving."

Table 9. Slit lamp microscopy findings of Grade >1 (events)

Treatment group	Adverse event	BL*	1 week	1 month	6 months	12 months	18 months	24 months	30 months	36 months	Unscheduled	Total
Control	Corneal staining	2	3	0	0	1	0	0	0	0	0	6
	Conjunctival staining	1	0	0	0	6	0	1	0	0	0	8
	Bulbar conjunctival hyperaemia	2	6	5	0	0	0	0	0	2	0	15
	Limbal hyperaemia	0	0	1	0	0	0	0	0	0	0	1
	Palpebral conjunctival hyperaemia	13	5	12	0	4	2	0	4	0	1	41
	Palpebral conjunctiva abnormality	4	3	1	4	2	2	0	0	4	0	20
	Corneal neovascularisation	0	0	0	0	0	0	0	0	0	0	0
	Other	2	2	0	0	0	0	0	0	0	0	4
MiSight	Corneal staining	0	10	4	0	0	0	0	0	0	0	14
	Conjunctival staining	1	4	4	7	4	0	0	1	0	1	22
	Bulbar conjunctival hyperaemia	0	2	0	2	0	2	2	0	0	3	11
	Limbal hyperaemia	0	1	0	1	0	2	0	0	0	1	5
	Palpebral conjunctival hyperaemia	13	6	9	8	5	7	4	2	0	2	56
	Palpebral conjunctiva abnormality	10	2	6	0	5	6	4	0	2	5	40
	Corneal neovascularisation	0	0	0	0	0	0	0	0	0	1	0
	Other	0	0	0	0	1	0	0	0	0	2	1

* Baseline

Table 10. Incidences of slit lamp microscopy findings of Grade >1 (events)

Treatment group	Cumulative incidence of eyes with findings % [95% CI] (Number of eyes)	Incidence of visits with findings % [95% CI]*1 (Number of visits)	Incidence rate of visits with findings per 100 person-years [95% CI]*2 (Number of visits/years of evaluation)
Control	30.1 [23.1, 38.3] (41/136)	7.2 [5.3, 9.8] (38/526)	20.8 [15.5, 27.2] (38/183)
MiSight	47.7 [39.2, 56.3] (61/128)	12.6 [9.9, 15.8] (62/493)	35.8 [29.1, 43.2] (62/173)
Total	38.6 [33.0, 44.6] (102/264)	9.8 [8.1, 11.8] (100/1019)	28.1 [23.7, 33.0] (100/356)

*1 Only the unscheduled visits where slit lamp microscopy was performed were included.
*2 Calculated by dividing the number of visits with at least 1 finding of Grade >1 by the years of evaluation.

6.A.(a).(3).2) Subjective symptoms of visual disorders

The occurrence of ghost images (double images), halos (luminous ring), and glare (dazzle) during the use of MiSight was assessed using a questionnaire on a 5-point scale of "Not noticeable," "Not annoying," "Slightly annoying," "Annoying," and "Very annoying." As a result, 5.9% (4 of 68) of the patients in the MiSight group and 3.1% (2 of 64) of the patients in the control group responded "Annoying" or "Very annoying."

6.A.(a).(3).3) Adverse events and malfunctions

Adverse events were observed in 23.1% (15 of 65) of patients in the MiSight group and 15.7% (11 of 70) of patients in the control group. Serious adverse events were observed in 3.1% (2 of 65) of patients in the MiSight group (seizure in 1 patient and hyperglycaemia in 1 patient) and 1.4% (1 of 70) of patients in the control group (illness requiring surgery in 1 patient). However, the causal relationship to the test device was ruled out in all of the events. Among all of the adverse events, those for which the causal relationship to the test device cannot be ruled out occurred in 13.8% (9 of 65) of patients in the MiSight group (corneal infiltrates in 1 patient, corneal neovascularization in 1 patient, corneal staining in 2 patients, conjunctivitis in 1 patient, subconjunctival haemorrhage in 1 patient, ocular inflammation in 1 patient, subconjunctival hyperaemia in 1 patient, tarsal hyperaemia in 1 patient, localized allergic reaction in 1 patient, eye pain in 1 patient, and headache in 1 patient) (some subjects experienced more than 1 event) and 11.4% (8 of 70) of patients in the control group (corneal infiltrates in 2 patients, epithelial opalescence in 1 patient, corneal staining in 1 patient, conjunctivitis in 1 patient, subconjunctival hyperaemia in 1 patient, tarsal hyperaemia in 1 patient, localized allergic reaction in 1 patient, eye pain in 1 patient, and headache in 1 patient) (some subjects experienced more than 1 event). All of the events were confirmed to have resolved.

A total of 8 malfunctions were reported in the MiSight group (2 events of lens breakage, 2 events of poor labeling in the secondary package, 1 event of lens thickness defect, 1 event of missing lens in the secondary package, and 2 events of temporary subjective symptoms [irritation and poor lens fitting due to lens placement]); and 4 malfunctions in the control group (1 event of lens breakage, 1 event of foreign matter contamination, 1 event of insufficient power [poor visual acuity], and 1 event of erroneous number of lenses in the primary package [containing 2 lenses]). No malfunction-related injuries due to malfunctions were observed.

6.A.(a).(4) Other

Autorefraction spherical equivalent during fixation to each distance was measured to evaluate effects of the MiSight lens wear on accommodative response. The measurement results are shown in Table 11. There were no clear differences in the autorefraction spherical equivalent at both the visual distances between the MiSight and control groups at baseline as well as at 1, 2, and 3 years of lens wear.

Table 11. Autorefraction spherical equivalent (D) during fixation to each distance

Evaluation time point	Distance to object (m)	Treatment group	Number of eyes	Autorefraction spherical equivalent
Baseline	0.33	Control	74	-1.82 ± 0.47
		MiSight	70	-1.73 ± 0.50
	0.25	Control	74	-2.69 ± 0.78
		MiSight	70	-2.61 ± 0.63
	0.20	Control	74	-3.50 ± 0.73
		MiSight	70	-3.42 ± 0.83
At 1 year	0.33	Control	60	-1.96 ± 0.41
		MiSight	58	-1.86 ± 0.49
	0.25	Control	60	-2.70 ± 0.58
		MiSight	58	-2.70 ± 0.56
	0.20	Control	60	-3.67 ± 0.77
		MiSight	58	-3.58 ± 0.79
At 2 years	0.33	Control	60	-1.86 ± 0.45
		MiSight	55	-1.84 ± 0.52
	0.25	Control	60	-2.75 ± 0.54
		MiSight	55	-2.60 ± 0.47
	0.20	Controlp	60	-3.55 ± 0.60
		MiSight	55	-3.51 ± 0.57
At 3 years	0.33	Control	56	-1.93 ± 0.63
		MiSight	52	-1.95 ± 0.47
	0.25	Control	56	-2.68 ± 0.65
		MiSight	52	-2.73 ± 0.51
	0.20	Control	56	-3.56 ± 0.83
		MiSight	52	-3.50 ± 0.69

Mean ± SD

6.A.(b) MIST401 (Part 2) study (NCT No. 01729208; study period, [redacted] 20[redacted] to [redacted] 20[redacted])

An unmasked, single-arm study was conducted at 4 study sites in foreign countries (Portugal, the UK, Singapore, and Canada) to investigate the long-term efficacy and safety of MiSight in patients who completed the MIST401 (Part 1) study and gave their informed consent to participate in the MIST401 (Part 2) study. In this study, all of the patients assigned to the MiSight group and control group in the MIST401 (Part 1) study were to wear MiSight for 3 years (hereinafter, the group in which the patients were to use the MiSight lens for 6 years, i.e., both in the MIST401 (Part 1) and MIST401 (Part 2) studies is referred to as “T6 group,” and the group in which the patients were to use the MiSight lens for 3 years after using the control lens for 3 years as “T3 group”).

Figure 5 shows patient disposition in the MIST401 (Part 2) study. From the MIST401 (Part 1) study, 108 patients entered in this study (52 in the T6 group and 56 in the T3 group), and all of the patients were included in the efficacy and safety analysis sets. The study was discontinued prematurely in 16 patients (6 in the T6 group and 10 in the T3 group) and the common reasons for discontinuation were consent withdrawal in 6 patients (3 in the T6 group and 3 in the T3 group) and poor visual acuity in 5 patients (1 in the T6 group and 4 in the T3 group).

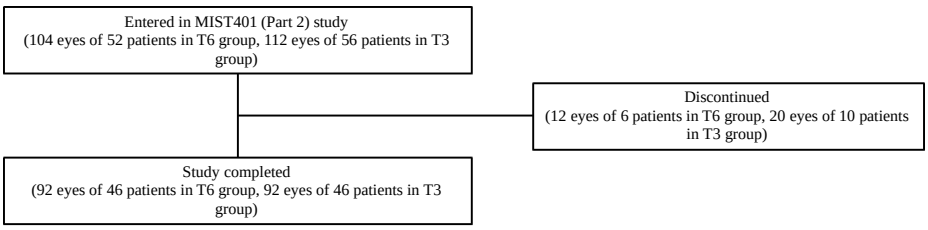

Figure 5. Patient disposition

6.A.(b).(1) Patient characteristics

Table 12 shows the characteristics of patients enrolled in the study.

Table 12. Patient characteristics

Item		T3 (112 eyes of 56 patients)	T6 (104 eyes of 52 patients)
Sex	Male	48% (27 patients)	54% (28 patients)
	Female	52% (29 patients)	46% (24 patients)
Age (years)*		13.0 ± 1.5	13.2 ± 1.3
Cycloplegic spherical power (D)*		-3.20 ± 1.14	-2.18 ± 0.97
Cycloplegic cylinder power (D)*		-0.49 ± 0.26	-0.67 ± 0.40
Cycloplegic autorefraction spherical equivalent (D)*		-3.45 ± 1.14	-2.52 ± 0.98
Axial length (mm)*		25.07 ± 0.74	24.76 ± 0.66

* Mean ± SD

6.A.(b).(2) Efficacy

6.A.(b).(2).1) Primary endpoint

Tables 13 and 15 show changes from baseline in cycloplegic autorefraction spherical equivalent and axial length. As shown in Tables 14 and 16, the changes from baseline in cycloplegic autorefraction spherical equivalent and axial length in the MIST401 (Part 1) study were similar to those in the MIST401 (Part 2) study in patients in the T6 group who wore the MiSight lens for 6 years from the MIST401 (Part 1) study through the MIST401 (Part 2) study, suggesting the long-term efficacy of MiSight.

Table 13. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

Study	Evaluation time point	Treatment group	Number of eyes	Autorefraction spherical equivalent	Change in autorefraction spherical equivalent
MIST401 (Part 1)	Baseline	T3	112	-2.21 ± 0.83	-
		T6	104	-2.01 ± 0.77	-
	At 1 year	T3	110	-2.79 ± 1.04	-0.58 ± 0.42
		T6	102	-2.19 ± 0.85	-0.18 ± 0.39
	At 2 years	T3	112	-3.15 ± 1.11	-0.94 ± 0.52
		T6	102	-2.33 ± 0.94	-0.35 ± 0.52
	At 3 years	T3	112	-3.45 ± 1.14	-1.24 ± 0.61
		T6	104	-2.52 ± 0.98	-0.51 ± 0.64
MIST401 (Part 2)	At 4 years	T3	102	-3.59 ± 1.17	-1.37 ± 0.66
		T6	98	-2.70 ± 1.00	-0.69 ± 0.68
	At 5 years	T3	98	-3.73 ± 1.24	-1.54 ± 0.75
		T6	96	-2.88 ± 1.16	-0.86 ± 0.85
	At 6 years	T3	90	-3.80 ± 1.30	-1.55 ± 0.81
		T6	80	-2.92 ± 1.13	-0.92 ± 0.87

Mean ± SD

Table 14. Comparison of changes in cycloplegic autorefraction spherical equivalent (D) from baseline between MIST401 (Part 1) and MIST401 (Part 2) studies

Treatment group	MIST401	Change in autorefraction spherical equivalent	Between-group difference*	95% CI*
T6	Year 1 in Part 2 study	-0.21 ± 0.08	0.02 ± 0.08	-0.13, 0.17
	Year 1 in Part 1 study	-0.23 ± 0.08		
	Year 2 in Part 2 study	-0.34 ± 0.08	0.05 ± 0.08	-0.10, 0.19
	Year 2 in Part 1 study	-0.39 ± 0.08		
	Year 3 in Part 2 study	-0.51 ± 0.08	0.01 ± 0.08	-0.14, 0.16
	Year 3 in Part 1 study	-0.52 ± 0.08		
T3	Year 1 in Part 2 study	-0.13 ± 0.08	0.52 ± 0.07	0.38, 0.66
	Year 1 in Part 1 study	-0.66 ± 0.08		
	Year 2 in Part 2 study	-0.28 ± 0.08	0.73 ± 0.07	0.59, 0.88
	Year 2 in Part 1 study	-1.02 ± 0.08		
	Year 3 in Part 2 study	-0.34 ± 0.08	0.98 ± 0.07	0.84, 1.12
	Year 3 in Part 1 study	-1.32 ± 0.08		

Least squares mean ± SE

* Analysis using a linear mixed-effects model with group, examination, study, and study site as fixed factors; group-by-study site, group-by-examination, group-by-study, and group-by-examination-by-study as interactions; age at baseline, myopia at baseline (autorefraction spherical equivalent or axial length), and ethnicity as covariates; and subject (by study site) and eyes (by subject) as random factors

Table 15. Change in axial length from baseline (mm)

Study	Evaluation time point	Treatment group	Number of eyes	Axial length	Change in axial length
MIST401 (Part 1)	Baseline	T3	112	24.44 ± 0.71	-
		T6	104	24.46 ± 0.68	-
	At 1 year	T3	110	24.71 ± 0.67	0.24 ± 0.16
		T6	102	24.54 ± 0.66	0.09 ± 0.14
	At 2 years	T3	112	24.90 ± 0.72	0.46 ± 0.24
		T6	102	24.63 ± 0.64	0.20 ± 0.22
	At 3 years	T3	112	25.07 ± 0.74	0.62 ± 0.30
		T6	104	24.76 ± 0.66	0.30 ± 0.28
MIST401 (Part 2)	At 4 years	T3	102	25.13 ± 0.73	0.71 ± 0.34
		T6	98	24.87 ± 0.64	0.37 ± 0.31
	At 5 years	T3	98	25.19 ± 0.73	0.77 ± 0.38
		T6	96	24.94 ± 0.65	0.44 ± 0.36
	At 6 years	T3	90	25.25 ± 0.76	0.81 ± 0.43
		T6	80	24.95 ± 0.59	0.49 ± 0.39

Mean ± SD

Table 16. Comparison of changes in axial length from baseline (mm) between MIST401 (Part 1) and MIST401 (Part 2) studies

Treatment group	MIST401	Change in axial length	Between-group difference*	95% CI*
T6	Year 1 in Part 2 study	0.08 ± 0.03	-0.01 ± 0.03	-0.08, 0.05
	Year 1 in Part 1 study	0.09 ± 0.03		
	Year 2 in Part 2 study	0.15 ± 0.03	-0.04 ± 0.03	-0.10, 0.03
	Year 2 in Part 1 study	0.19 ± 0.03		
	Year 3 in Part 2 study	0.23 ± 0.03	-0.05 ± 0.03	-0.11, 0.01
	Year 3 in Part 1 study	0.28 ± 0.03		
T3	Year 1 in Part 2 study	0.05 ± 0.03	-0.20 ± 0.03	-0.26, -0.14
	Year 1 in Part 1 study	0.26 ± 0.03		
	Year 2 in Part 2 study	0.12 ± 0.03	-0.35 ± 0.03	-0.42, -0.29
	Year 2 in Part 1 study	0.47 ± 0.03		
	Year 3 in Part 2 study	0.18 ± 0.03	-0.46 ± 0.03	-0.52, -0.40
	Year 3 in Part 1 study	0.64 ± 0.03		

Least squares mean ± SE

* Analysis using a linear mixed-effects model with group, examination, study, and study site as fixed factors; group-by-study site, group-by-examination, group-by-study, and group-by-examination-by-study as interactions; age at baseline, myopia at baseline (autorefraction spherical equivalent or axial length), and ethnicity as covariates; and subject (by study site) and eyes (by subject) as random factors

6.A.(b).(2).2) Corrected visual acuity with contact lens

Figure 6 shows the distance visual acuity with contact lens wear. There was no clear difference between the T6 and T3 groups.

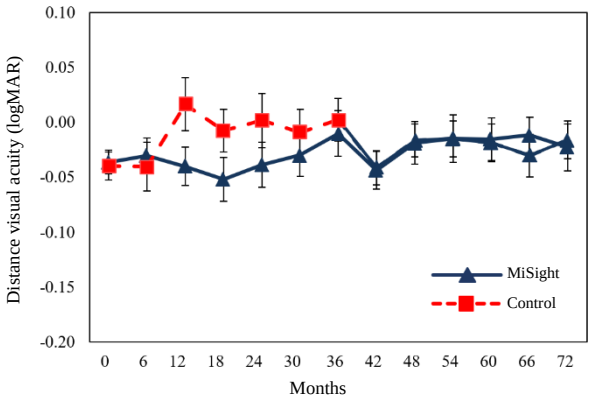

Figure 6. Corrected visual acuity with contact lens

6.A.(b).(3) Safety

6.A.(b).(3).1) Slit lamp microscopy findings

Table 17 shows slit lamp microscopy findings of Grade >1. There was no trend towards an increase in number of events over time. As shown in Table 18, the incidences of events were 17.0% (17 of 100 patients) in the T6 group and 6.0% (6 of 100 patients) in the T3 group. The incidence rates per 100 person-years adjusted according to the total wearing time was 7.5 in the T6 group and 3.3 in the T3 group. In the T6 group, 1 patient experienced Grade 3 bulbar hyperaemia, and Grade 3 palpebral conjunctival hyperaemia occurred in the same patient. However, these events did not lead to study discontinuation, and the outcomes were reported as “resolved.”

Table 17. Slit lamp microscopy findings of Grade >1 (events)

Treatment group	Adverse event	42 months	48 months	54 months	60 months	66 months	72 months	Unscheduled	Total
T3	Corneal staining	1	0	1	0	0	0	0	2
	Conjunctival staining	0	0	0	0	0	0	0	0
	Bulbar conjunctival hyperaemia	0	1	0	0	0	0	0	1
	Limbal hyperaemia	0	0	0	0	0	0	0	0
	Palpebral conjunctival hyperaemia	0	0	0	0	0	2	0	2
	Palpebral conjunctiva abnormality	0	0	0	0	0	0	1	1
	Corneal neovascularisation	0	0	0	0	0	0	0	0
	Other	0	0	0	0	0	0	0	0
T6	Corneal staining	2	0	0	0	0	0	0	2
	Conjunctival staining	1	0	0	0	0	1	0	2
	Bulbar conjunctival hyperaemia	0	2	0	0	1	0	2	5
	Limbal hyperaemia	0	2	0	0	0	0	0	2
	Palpebral conjunctival hyperaemia	0	2	0	2	0	0	6	10
	Palpebral conjunctiva abnormality	2	0	0	0	0	0	8	10
	Corneal neovascularisation	0	0	0	0	0	0	0	0
	Other	0	0	0	0	0	0	0	0

Table 18. Incidences of slit lamp microscopy findings of Grade >1 (events)

Treatment group	Cumulative incidence of eyes with findings % [95% CI] (Number of eyes)	Incidence of visits with findings % [95% CI][*1] (Number of visits)	Incidence rate of visits with findings per 100 person-years [95% CI][*2] (Number of visits/years of evaluation)
T3	6.0 [2.8, 12.5] (6/100)	1.6 [0.7, 3.6] (5/320)	3.3 [1.4, 7.6] (5/150)
T6	17.0 [10.9, 25.5] (17/100)	3.6 [2.0, 6.3] (11/306)	7.5 [4.3, 13.0] (11/146)
Total	11.5 [7.8, 16.7] (23/200)	2.6 [1.6, 4.1] (16/626)	5.4 [3.4, 8.6] (16/296)

*1 Only the unscheduled visits where slit lamp microscopy was performed were included.
*2 Calculated by dividing the number of visits with at least 1 finding of Grade >1 by the years of evaluation.

6.A.(b).(3).2 Subjective symptoms of visual disturbance

The occurrence of ghost images (double images), halos (luminous ring), and glare (dazzle) during the use of MiSight was evaluated using a questionnaire on a 5-point scale of “Not noticeable,” “Not annoying,” “Slightly annoying,” “Annoying,” and “Very annoying.” As a result, 4.0% (2 of 50) of patients in the T6 group and 0% (0 of 50) of patients in the T3 group responded “Annoying” or “Very annoying.”

6.A.(b).(3).3 Adverse events and malfunctions

Adverse events were reported in 20.4% (22 of 108) of patients. Serious adverse events were reported in 6.5% (7 of 108) of patients (corneal ulcer and scar in 1 patient, scar in 1 patient, uveitis in 1 patient, illness requiring appendectomy in 1 patient, illness requiring spinal surgery in 1 patient, Stevens-Johnson syndrome in 1 patient, and fracture in 1 patient). Of these events, a causal relationship to the test device could not be ruled out in 3 patients (corneal ulcer and scar in 1 patient, scar in 1 patient, and uveitis in 1 patient). The outcome of uveitis in 1 patient was reported as “resolved,” while those of corneal ulcer and scar in 1 patient and scar in 1 patient were reported as “unchanged.” Adverse events for which a causal relationship to the test device cannot be ruled out, including non-serious events, occurred in 12.0% (13 of 108) of patients (corneal ulcer and scar in 1 patient, scar in 1 patient, giant papillary conjunctivitis in 2 patients, meibomitis in 1 patient, hyperaemia in 1 patient, eye pain and irritation in 3 patients, burning sensation in 1 patient, sensation of foreign body in 2 patients, and poor lens fitting in 3 patients) (some subjects experienced more than 1 event). All of these events resolved, except for corneal ulcer and scar in 1 patient and scar in 1 patient.

In addition, there were 2 malfunctions, and both were temporary subjective symptoms caused by the lens wear (irritation and poor lens fitting). No malfunction-related injuries were observed.

6.A.(c) MIST402 study (NCT No. 05779072; study period, March 2019 to March 2021)

An unmasked, single-arm study was conducted at 4 study sites in foreign countries (Portugal, UK, Singapore, and Canada) to investigate levels of myopia progression after completion of the MiSight lens wear in patients who completed the MIST401 (Part 2) study and gave their informed consent to participate in the MIST402 study. In this study, the patients who completed the MIST401 (Part 2) study were to wear the approved product “Proclear 1 Day” for 1 year.

Figure 7 shows patient disposition in the MIST402 study. A total of 83 patients from the MIST401 (Part 2) study (43 in the T6 group and 40 in the T3 group) entered in this study. The population excluding 5

patients who had no data on the primary endpoint was included in the efficacy analysis set. The study was discontinued prematurely in 7 patients (6 in the T6 group and 1 in the T3 group) and the common reason for discontinuation were poor visual acuity in 4 patients (4 in the T6 group and 1 in the T3 group) and consent withdrawal in 1 patient (the T6 group).

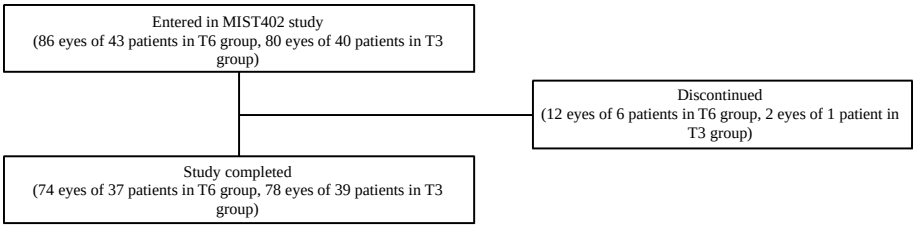

Figure 7. Patient disposition

6.A.(c).(1) Patient characteristics

Table 19 shows the characteristics of patients enrolled in the study.

Table 19. Patient characteristics

Item		T3 (80 eyes of 40 patients)	T6 (86 eyes of 43 patients)
Sex	Male	50% (20 patients)	51% (22 patients)
	Female	50% (20 patients)	49% (21 patients)
Age (years)*		16.1 ± 1.6	16.3 ± 1.2
Cycloplegic spherical power (D)*		-3.50 ± 1.26	-2.74 ± 1.16
Cycloplegic cylinder power (D)*		-0.70 ± 0.42	-0.81 ± 0.52
Cycloplegic autorefraction spherical equivalent (D)*		-3.85 ± 1.23	-3.14 ± 1.21
Axial length (mm)*		25.33 ± 0.76	25.07 ± 0.70

* Mean ± SD

6.A.(c).(2) Efficacy

1) Primary endpoint

Table 20 and Figure 8 show the results of changes in cycloplegic autorefraction spherical equivalent. Table 21 and Figure 9 show the results of changes in axial length. No rapid myopia progression associated with entry in the MIST402 study after completion of the MIST401 (Part 2) study was observed [see Section “6.B.(6) Myopia progression due to discontinuation of the MiSight lens wear”].

Table 20. Annualized change from baseline in cycloplegic autorefraction spherical equivalent (D)

Study	Treatment group	Number of eyes	Change in autorefraction spherical equivalent
MIST401 (Part 1)	T3	80	-0.41 ± 0.19
	T6	76	-0.18 ± 0.21
MIST401 (Part 2)	T3	80	-0.10 ± 0.18
	T6	76	-0.17 ± 0.14
MIST402	T3	80	-0.23 ± 0.36
	T6	76	-0.21 ± 0.40

Mean ± SD

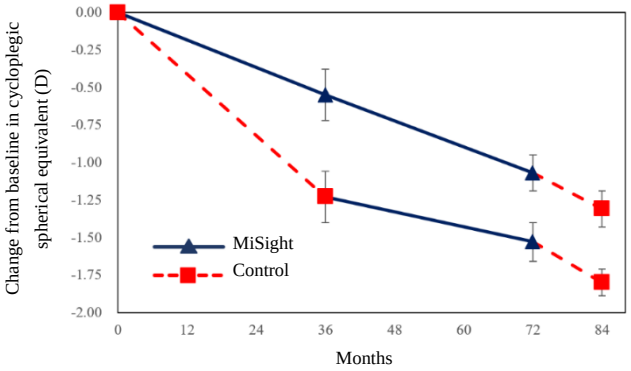

Figure 8. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

Table 21. Annualized change in axial length (mm)

Study	Treatment group	Number of eyes	Change in axial length
MIST401 (Part 1)	T3	80	0.21 ± 0.10
	T6	76	0.10 ± 0.10
MIST401 (Part 2)	T3	80	0.06 ± 0.08
	T6	76	0.08 ± 0.06
MIST402	T3	80	0.09 ± 0.09
	T6	76	0.10 ± 0.10

Mean ± SD

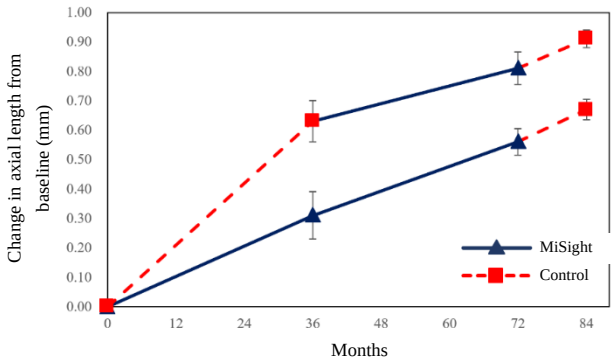

Figure 9. Change in axial length from baseline (mm)

6.A.(d) MIST-J study (jRCT No. 2052210116; study period, [redacted]20[redacted] to [redacted] 20[redacted])

To confirm the extrapolability of foreign clinical study data, a randomized, double-masked, parallel-group study was conducted at 3 study sites in Japan in order to evaluate the efficacy and safety of MiSight versus the approved product “Proclear 1 Day” in patients aged 8 to 12 years with low-to-moderate myopia. Table 22 shows the summary of the study.

Table 22. Summary of MIST-J study

Study	MIST-J study
Study design	Randomized, double-masked, parallel-group study
Inclusion criteria	(1) Subjects who [redacted] (2) Subjects aged 8 to 12 years at the time of screening (3) Subjects who have read a consent document for subjects, been given an explanation, understood its content, and voluntarily given their consent to participate in the study (4) The subject's legally acceptable representative has read aa consent document for the legally acceptable representative, been given an explanation, understood its content, and signed the informed consent. (5) Along with their legally acceptable representative, subjects who are capable of comprehending the nature of the study and are willing to adhere to the rules (6) Along with their legally acceptable representative, subjects who are willing to voluntarily cooperate to adhere to the study plans including the follow-up schedule (7) Subjects who have agreed to accept treatment as assigned by the randomization (8) Subjects who are willing to agree to wear the study lenses for a minimum of 10 hours per day, at least 6 days per week during the study period. In addition, those who can agree to report to the investigator when the lens wear schedule is interrupted. (9) Subjects who possess visually functional eyeglasses or are able to have the eyeglasses prepared before starting the study lens wear (10) Subjects who are in good general health, based on the subject's and the legally acceptable representative's knowledge (11) Subjects with best-corrected visual acuity of ≥+0.10 logMAR in each eye (12) Subjects who have spherical equivalent between −0.75 and−-4.00 D, astigmatism ≤−0.75 D, and a refractive difference between the right and left eyes <1.00 D in a cycloplegic refraction measured using an autorefractometer at screening
Exclusion criteria	(1) Subjects who appear to exhibit poor personal hygiene (2) Subjects who are currently participating or participated within 30 days in another clinical study (clinical trial) during the study period (3) The legally acceptable representative of the subject is a member of the study site staff, including the investigator(s). (4) Subjects who have previously worn hard contact lenses (including rigid gas permeable contact lenses), including orthokeratology lenses (5) Subjects with current or prior use of any myopia progression control treatment such as bifocals, progressive addition lenses, and atropine (6) Subjects who were born earlier than 30 weeks or weighed less than 1500 g at birth (7) Subjects who regularly use ocular medications (prescription or over-the-counter), including artificial tears (8) Subjects with current use of medications which may significantly affect contact lens wear, tear film production, pupil size, accommodation or refractive state. The following medications are given as examples, but not limited to; long-term use of nasal decongestants (e.g., pseudoephedrine, phenylephrine), antihistamines (chlorpheniramine, diphenhydramine), prednisolone, or Ritalin (methylphenidate). (9) Subjects with a known allergy to fluorescein or cyclopentolate hydrochloride (10) Subjects with a history of corneal hypoesthesia (reduced corneal sensitivity), corneal ulcer, corneal infiltrates, infective ocular inflammation, or other recurrent ocular inflammation (11) Subjects diagnosed with strabismus (12) Subjects with known ocular or systemic illness, such as, but not limited to; anterior uveitis, iritis, episcleritis, scleritis, glaucoma, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, and diabetes mellitus. (13) Subjects with any ocular, systemic, or neuro-developmental conditions that could influence vision development. Such as, but not limited to; persistent pupillary membrane, vitreous haemorrhage, cataract, corneal scar, eyelid ptosis due to haemangioma, Marfan's syndrome, Down's syndrome, Ehlers-Danlos syndrome, Stickler's syndrome, ocular albinism, or retinopathy of prematurity. (14) Subjects with keratoconus or an irregular corneal shape (15) Subjects with slit lamp microscopy findings that would contraindicate contact lens wear, including: • Corneal scars within the visual axis • Neovascularization or ghost vessel formation in ≥1.5 mm from the corneal limbus • Any active anterior segment ocular illness that would contraindicate contact lens wear • Abnormal palpebral conjunctiva findings of Grade ≥2 • Allergic or seasonal conjunctivitis • At least one of the following abnormal findings is Grade 3 or 4: Bulbar conjunctival and limbal hyperaemia, palpebral conjunctival hyperaemia, corneal staining (type), and conjunctival staining (16) The investigator considers that it is not in the best interest of the subject to participate in the study.

Target sample size	120 eyes of 60 patients (60 eyes of 30 patients in the MiSight group and 60 eyes of 30 patients in the control group) The required sample size was calculated to be [redacted] patients under the conditions of two-sided significance level of 5%, power of [redacted]%, standard deviation of [redacted] D, and detection of therapeutic efficacy of [redacted] D/year. Assuming an annual dropout rate of [redacted]%, the target sample size was determined to be 60 patients.
Directions for use	Daily wear, daily disposable The contact lenses are to be worn for a minimum of 10 hours and a maximum of 15 hours per day, at least 6 days per week. In the measurement of corrected visual acuity with contact lens (distant vision), any change of the lens power should be considered with reference to manifest refraction values if additional correction of ≥±0.50 D is required.
Follow-up period	2 years (The primary endpoint was analyzed at 1 year.)
Endpoints	***Efficacy*** Change from baseline to 1 year in cycloplegic autorefraction spherical equivalent (primary endpoint) Change from baseline to 1 year in axial length (secondary endpoint) Corrected visual acuity with contact lens, etc. ***Safety*** Slit lamp microscopy findings, subjective symptoms related to visual disorders, corneal endothelial cells, adverse events, malfunctions, etc. ***Other*** Autorefraction spherical equivalent, etc. during fixation to each distance

Figure 10 shows patient disposition in the MIST-J study. The MIST-J study enrolled 62 patients and all of them were randomized. Of the randomized population, 2 patients who discontinued the study before the start of lens wear (1 in the MiSight group and 1 in the control group) were excluded, and the remaining patients were included in the efficacy and safety analysis sets. One patient in the MiSight group discontinued the study after the start of lens wear due to the consent withdrawal.

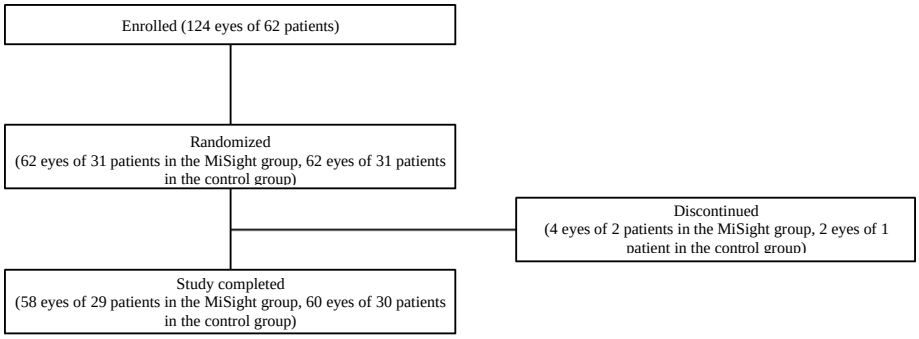

Figure 10. Patient disposition

6.A.(d).(1) Patient characteristics

There was no clear difference in the patient characteristics between the MiSight and control groups as shown in Table 23.

Table 23. Patient characteristics

Item		Product (60 eyes of 30 patients)	Control (60 eyes of 30 patients)
Sex	Male	50% (15 patients)	53% (16 patients)
	Female	50% (15 patients)	47% (14 patients)
Age (years)*		10.3 ± 1.3	10.5 ± 1.3
Cycloplegic spherical power (D)*		-1.87 ± 0.72	-2.11 ± 0.70
Cycloplegic cylinder power (D)*		-0.36 ± 0.22	-0.32 ± 0.25
Cycloplegic autorefraction spherical equivalent (D)*		-2.05 ± 0.70	-2.27 ± 0.72
Axial length (mm)*		24.45 ± 0.61	24.49 ± 0.64

* Mean ± SD

6.A.(d).(2) Efficacy

6.A.(d).(2).1) Primary endpoint

Table 24 and Figure 11 show the results of change from baseline in cycloplegic autorefraction spherical equivalent. The study demonstrated the superiority of MiSight over the control.

Table 24. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

Evaluation time point	Treatment group	Number of eyes	Autorefraction spherical equivalent	Change in autorefraction spherical equivalent	Between-group difference [95% CI]*1,*2	*P*-value*2,*3
Baseline	Control	60	-2.27 ± 0.72	-	-	-
	MiSight	60	-2.05 ± 0.70	-		
At 1 year	Control	60	-3.07 ± 0.89	-0.80 ± 0.45	0.42 [0.22, 0.63]	0.0001
	MiSight	58	-2.46 ± 0.99	-0.38 ± 0.47		

Mean ± SD

*1 Difference in adjusted mean

*2 Analysis using a linear mixed model with the study device (test device/comparator), eyes (right eye/left eye), age (≤10 years/≥11 years), sex (male/female), and values at screening as fixed factors, and subjects as random factors. Given the small sample size, the Kenward-Roger method was used to adjust the degrees of freedom.

*3 A two-sided significance level of 5%

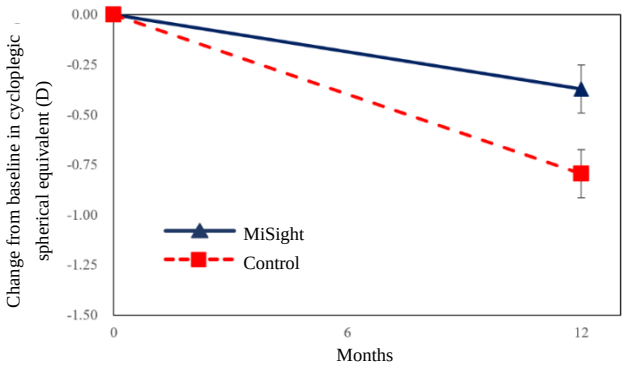

Figure 11. Change from baseline in cycloplegic autorefraction spherical equivalent (D)

6.A.(d).(2).2) Secondary endpoint

Table 25 and Figure 12 show the results of change from baseline in axial length, supporting the results of the primary endpoint.

Table 25. Change in axial length from baseline (mm)

Evaluation time point	Treatment group	Number of eyes	Axial length	Change in axial length	Between-group difference [95% CI][*1,*2]
Baseline	Control	60	24.49 ± 0.64	-	-
	MiSight	60	24.45 ± 0.61	-	
At 1 year	Control	60	24.83 ± 0.66	0.34 ± 0.16	-0.19 [-0.27, -0.11]
	MiSight	58	24.60 ± 0.66	0.16 ± 0.18	

Mean ± SD
*1 Difference in adjusted mean
*2 Analysis using a linear mixed model with the study device (test device/comparator), eyes (right eye/left eye), age (≤10 years/≥11 years), sex (male/female), and values at screening as fixed factors, and subjects as random factors. Given the small sample size, the Kenward-Roger method was used to adjust the degrees of freedom.

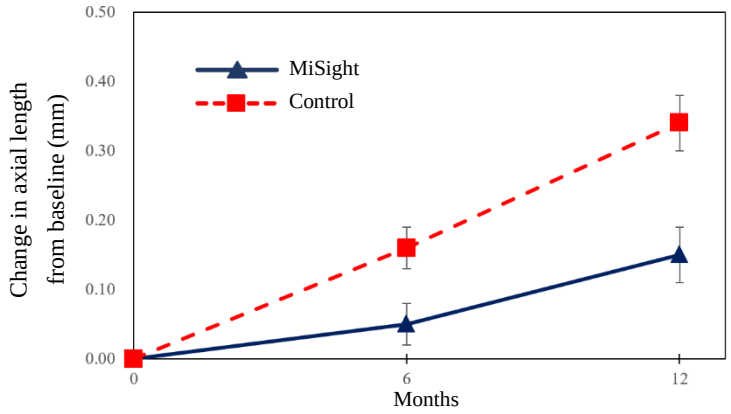

Figure 12. Change in axial length from baseline (mm)

3) Corrected visual acuity with contact lens

Table 26 shows corrected visual acuity with contact lens. Throughout the study period, mean distance visual acuity was ≤0.06 logMAR (equivalent to decimal visual acuity of ≥0.86) in both groups. Mean near visual acuity was ≤−0.08 logMAR (equivalent to decimal visual acuity of ≥1.19) in both groups. Mean additional correction of distance visual acuity was ≤−0.11 logMAR (equivalent to decimal visual acuity of ≥1.30) in both groups.

Table 26. Contact lens-corrected visual acuity (logMAR)

Evaluation time point	Treatment group	Number of eyes	Distance vision	Near vision	Additional correction of distance vision
Baseline	Control	60	-0.09 ± 0.09	-0.09 ± 0.10	-0.15 ± 0.09
	MiSight	60	-0.04 ± 0.09	-0.08 ± 0.11	-0.12 ± 0.09
At 1 week	Control	60	-0.05 ± 0.13	-0.09 ± 0.11	-0.13 ± 0.10
	MiSight	59	-0.03 ± 0.16	-0.09 ± 0.11*	-0.14 ± 0.11*
At 1 month	Control	60	-0.05 ± 0.10	-0.10 ± 0.11	-0.14 ± 0.09
	MiSight	58	-0.05 ± 0.11	-0.09 ± 0.11	-0.13 ± 0.09
At 3 months	Control	60	-0.03 ± 0.16	-0.11 ± 0.12	-0.13 ± 0.11
	MiSight	56	-0.05 ± 0.10	-0.12 ± 0.10	-0.12 ± 0.09
At 6 months	Control	60	-0.01 ± 0.13	-0.12 ± 0.11	-0.14 ± 0.09
	MiSight	60	-0.05 ± 0.12	-0.12 ± 0.10	-0.15 ± 0.09
At 9 months	Control	60	0.01 ± 0.13	-0.14 ± 0.09	-0.12 ± 0.09
	MiSight	58	-0.02 ± 0.12	-0.11 ± 0.11	-0.13 ± 0.09
At 1 year	Control	60	0.06 ± 0.13	-0.12 ± 0.11	-0.11 ± 0.08
	MiSight	58	-0.01 ± 0.15	-0.13 ± 0.10	-0.12 ± 0.09

Mean ± SD
* 58 eyes

6.A.(d).(3) Safety

6.A.(d).(3).1) Slit lamp microscopy findings

Slit lamp microscopy findings of Grade >1 were observed only in 1.7% (1 of 60) of patients in the MiSight group, and that was Grade 2 hordeolum in 1 patient. The causal relationship to the study device was ruled out. The event was non-serious and resolved after treatment with antibiotics.

6.A.(d).(3).2) Subjective symptoms of visual disorders

The occurrence of ghost images (double images), halos (luminous ring), and glare (dazzle) during the use of MiSight was assessed using a questionnaire on a 5-point scale of "Not noticeable," "Noticeable but not annoying," "Slightly annoying," "Annoying," and "Very annoying." As a result, 16.7% (5 of 30) of patients in the MiSight group and 16.7% (5 of 30) of patients in the control group responded "Annoying" or "Very annoying."

6.A.(d).(3).3) Corneal endothelial cells

Cell density, coefficient of variation, and incidence of hexagonal cells were evaluated by corneal endothelial cell counting. The results are shown in Table 27. There was no clear change in each parameter in the MiSight group or control group.

Table 27. Corneal endothelial cells

Item	Treatment group	Evaluation time point	
		Baseline	At 1 year
Cell density (cells/mm^2)	Control	3,273.9 ± 223.0	3,264.2 ± 233.9
	MiSight	3,322.9 ± 244.8	3,316.7 ± 258.3
Coefficient of variation* (%)	Control	24.6 ± 3.0	25.6 ± 3.3
	MiSight	24.3 ± 3.1	26.0 ± 2.8
Incidence of hexagonal cells (%)	Control	67.6 ± 6.1	67.4 ± 6.8
	MiSight	67.8 ± 5.3	66.0 ± 5.3

Mean ± SD

* (SD of cell area/Mean cell area) ×100

6.A.(d).(3).4) Adverse events and malfunctions

Adverse events were reported in 86.7% (26 of 30) of patients (71 events) in the MiSight group and 96.7% (29 of 30) of patients (79 events) in the control group. There were no serious adverse events. Adverse events for which a causal relationship to the test device cannot be ruled out occurred in 3.3% (1 of 30) of patients in the MiSight group alone. The adverse events were 2 events of dry eye sensation which is a common event occurring during contact lens wear. The adverse events resolved without treatment.

Twenty-four malfunctions were reported in the MiSight group (16 events of lens breakage [tear, chipping], 6 events of foreign matters in the storage solution, 1 event of a package containing 2 lenses, 1 event of lens surface abnormality [foreign matter]), and 31 events in the control group (26 events of lens breakage [tear, chipping], 2 events of a package containing 2 lenses, 2 events of a package containing no lens, and 1 event of unknown). There were no malfunction-related injuries.

6.A.(d).(4) Other

Autorefraction spherical equivalent during fixation to each distance was measured to evaluate the impact of the MiSight lens wear on accommodative response. The measurement results are shown in Table 28.

There were no clear differences in the autorefraction spherical equivalent at any visual distance between the MiSight and control groups at 1 month or 1 year of lens wear.

Table 28. Autorefraction spherical equivalent (D) during fixation to each distance

Evaluation time point	Distance to object (m)	Treatment group	Number of eyes	Autorefraction spherical equivalent
At 1 month	0.33	Control	30	-1.97 ± 0.53
		MiSight	28	-1.85 ± 0.43
	0.25	Control	30	-2.75 ± 0.62
		MiSight	28	-2.70 ± 0.53
	0.20	Control	30	-3.59 ± 0.78
		MiSight	28	-3.50 ± 0.63
At 1 year	0.33	Control	30	-2.13 ± 0.83
		MiSight	28	-1.98 ± 0.47
	0.25	Control	30	-2.55 ± 0.79
		MiSight	28	-2.68 ± 0.78
	0.20	Control	30	-3.35 ± 0.99
		MiSight	28	-3.47 ± 0.81

Mean ± SD

6.B Outline of the review conducted by PMDA

PMDA considered that, among the submitted clinical evaluation data, the MIST401 (Part 1) study was the pivotal study to evaluate the efficacy and safety of MiSight and decided to evaluate the submitted data focusing on this study. In addition, PMDA decided to evaluate the efficacy and safety of MiSight in Japanese patients using clinical data from the MIST-J study. Furthermore, PMDA decided to evaluate the long-term safety of MiSight using data from the MIST401 (Part 2) study and to evaluate myopia progression due to discontinuation of MiSight wear using data from the MIST402 study. The issues presented in the subsections below were mainly reviewed based on the comments from the Expert Discussion.

6.B.(1) Clinical study design

PMDA asked the applicant to explain the rationale for the design of each clinical study.

The applicant's explanation:

At the time of designing the MIST401 (Part 1) study, there were no drugs or medical devices approved for slowing the progression of myopia. For this and other reasons, the applicant decided to demonstrate the superiority of MiSight over the monofocal contact lens "Proclear 1 Day" which differs only in the optical part design from MiSight.

The study population was decided to include patients aged ≥8 and ≤12 years, considering the age at which children are likely to be able to wear and remove their contact lenses by themselves and may experience more remarkable myopia progression. Since the lowest diopter required for children receiving vision correction for the first time was considered to be −0.75 D, this was selected as the lower limit. MiSight lenses were manufacturable up to −6.00 D at the time of designing the study; therefore, the upper limit of −4.00 D was selected, considering myopia progression during the study period.

Cycloplegic autorefraction spherical equivalent and axial length were selected as primary endpoints, because (i) autorefraction spherical equivalent is an index used for objective evaluation and measured

as an index of myopia progression in clinical settings, and (ii) myopia progression in childhood is caused by axial elongation. Assuming that the expected effects of slowing of myopia progression with MiSight would be 0.25 D/year based on the published literature[12] in which effects of slowing of myopia progression with bifocal contact lenses were evaluated, the clinically significant between-group difference was considered to be 0.75 D, and a 3-year study period was selected based on the opinion of medical experts.

In the MIST401 (Part 2) study, MiSight was provided to the patients who completed the MIST401 (Part 1) study in order to give the opportunity for treatment to the patients assigned to the control group in the MIST401 (Part 1) study and to evaluate the efficacy and safety of the MiSight lens wear for more than 3 years.

In the MIST402 study, patients who completed the MIST401 (Part 2) study were to wear the monofocal contact lens "Proclear 1 Day" for evaluation of the degree of myopia progression after completion of the MiSight lens wear.

Genetic and environmental factors are considered to be involved in myopia progression, and it has been reported that there is a difference in the rate of myopia progression between Japanese and non-Japanese populations.[13] For these and other reasons, the MIST-J study was designed to confirm the extrapolability of the clinical data from the MIST401 (Part 1) study to the Japanese population. This study was designed similarly to the MIST401 (Part 1) study, and it was intended to confirm the extrapolability of the clinical data of the MIST401 (Part 1) study to Japanese data by evaluating the efficacy of MiSight at 1 year in the Japanese patients.

PMDA's view:
There were no major problems with the design (control, intended patient population, primary endpoint, and follow-up period) of each clinical study. However, cycloplegic autorefraction spherical equivalent alone was selected as the primary endpoint in the MIST-J study. The axial length was also important in the evaluation of myopia progression in childhood. Therefore, PMDA decided to evaluate the efficacy of MiSight based on the axial length results as described in Section "6.B.(2) Efficacy."

6.B.(2) Efficacy

The applicant's explanation about the efficacy of MiSight:
The following results obtained in the MIST401 (Part 1) study has demonstrated the efficacy of MiSight in vision correction and slowing the progression of myopia:

- The MIST401 (Part 1) study verified the superiority of MiSight over the control in terms of the changes from baseline to 3 years in cycloplegic autorefraction spherical equivalent and axial length defined as the primary endpoints.
- Table 29 shows the proportion of eyes with myopia progression confirmed during the 3-year study period.

Table 29. Proportion of eyes with myopia progression over 3 years

Treatment group	Number of eyes	Myopia progression: Number of eyes (%)		Risk ratio [95% CI]
		≤-0.25 D	>-0.25 D	
Control	112	4 (4%)	108 (96%)	0.61 [0.52, 0.72]
MiSight	104	43 (41%)	61 (59%)	
		≤-0.50 D	>-0.50 D	
Control	112	11 (10%)	101 (90%)	0.50 [0.40, 0.62]
MiSight	104	57 (55%)	47 (45%)	
		≤-0.75 D	>-0.75 D	
Control	112	30 (27%)	82 (73%)	0.45 [0.33, 0.60]
MiSight	104	70 (67%)	34 (33%)	
		≤-1.00 D	>-1.00 D	
Control	112	43 (38%)	69 (62%)	0.30 [0.19, 0.46]
MiSight	104	85 (82%)	19 (18%)	

- Throughout the study period, corrected visual acuity with MiSight was generally a decimal visual acuity of ≥1.0 in both the distance and near vision.

The extrapolability of the foreign clinical data to Japanese patients was assessed. The results shown below indicate that the data of the MIST401 (Part 1) study can be extrapolated to Japanese patients. The results also suggest the efficacy of MiSight in vision correction and slowing the progression of myopia in Japanese patients.

- The MIST-J study verified the superiority of MiSight over the control in terms of the change from baseline to 1 year in cycloplegic autorefraction spherical equivalent defined as the primary endpoint.
- The change from baseline to 1 year in the axial length defined as the secondary endpoint also supported the results of the primary endpoint.
- Table 30 shows the proportion of eyes with myopia progression confirmed during the 1 year.

Table 30. Proportion of eyes with myopia progression over 1 year

Treatment group	Number of eyes	Myopia progression: Number of eyes (%)		Risk ratio [95% CI]
		≤-0.25 D	>-0.25 D	
Control	60	4 (6.7%)	56 (93.3%)	0.61 [0.48, 0.77]
MiSight	58	25 (43.1%)	33 (56.9%)	
		≤-0.50 D	>-0.50 D	
Control	60	17 (28.3%)	43 (71.7%)	0.53 [0.37, 0.76]
MiSight	58	36 (62.1%)	22 (37.9%)	
		≤-0.75 D	>-0.75 D	
Control	60	32 (53.3%)	28 (46.7%)	0.37 [0.20, 0.69]
MiSight	58	48 (82.8%)	10 (17.2%)	
		≤-1.00 D	>-1.00 D	
Control	60	42 (70.0%)	18 (30.0%)	0.52 [0.25, 1.06]
MiSight	58	49 (84.5%)	9 (15.5%)	

- In the MIST-J study, corrected visual acuity with MiSight was generally a decimal visual acuity of ≥1.0 in both the distance and near vision throughout the study period.

The point estimate of the difference in the change from baseline to 3 years in cycloplegic autorefraction spherical equivalent between the MiSight and control groups in the MIST401 (Part 1) study was 0.665 D, which was below the criterion for slowing myopia progression (0.75 D/3 years) that was considered clinically significant by the applicant at the time of designing the study. Thus, PMDA asked the applicant to explain the clinical significance of MiSight. PMDA also asked the applicant to explain the

extrapolability of the clinical data of the MIST401 (Part 1) study to Japanese patients based on the clinical data.

The applicant's explanation:
Although the study did not meet the criterion for slowing myopia progression (0.75 D/3 years) that considered clinically significant by the applicant at the time of designing the study, a 50% reduction in myopia progression has been reported to be of clinical significance.[14] The results of reduction rate in the MIST401 (Part 1) study satisfied this numerical threshold (Table 31). Since high myopia has been reported to increase risks of retinal detachment, myopic maculopathy, etc.,[15] that lead to visual disorders, slowing of myopia progression may lead to prophylaxis of these risks. Therefore, MiSight has been shown to have clinical significance.

Table 31. Changes from baseline in cycloplegic autorefraction spherical equivalent and axial length

Item	Evaluation time point	Treatment group	Number of eyes	Change from baseline	Reduction rate*
Cycloplegic autorefraction spherical equivalent (D)	1 year	Control	120	-0.58 ± 0.41	69%
		MiSight	116	-0.18 ± 0.39	
	2 years	Control	120	-0.92 ± 0.53	59%
		MiSight	110	-0.38 ± 0.52	
	3 years	Control	112	-1.24 ± 0.61	59%
		MiSight	104	0.51 ± 0.64	
Axial length (mm)	1 year	Control	120	0.24 ± 0.15	63%
		MiSight	116	0.09 ± 0.13	
	2 years	Control	120	0.45 ± 0.23	54%
		MiSight	110	0.21 ± 0.22	
	3 years	Control	112	0.62 ± 0.30	52%
		MiSight	104	0.30 ± 0.28	

Mean ± SD
* (The control group - the MiSight group)/the control group × 100

Table 32 shows changes in cycloplegic autorefraction spherical equivalent and axial length from baseline to 1 year in the MIST401 (Part 1) and MIST-J studies. Since no clear differences in the two parameters were observed between the 2 studies, the efficacy of MiSight is unlikely to differ between Japanese and non-Japanese patients.

Table 32. Changes from baseline to 1 year

Treatment group	Item	MIST401 (Part 1) study (Overseas)	MIST-J study (Japan)
Control	Autorefraction spherical equivalent (D)	-0.64 [-0.79, -0.50]	-0.79 [-0.94, -0.65]
	Axial length (mm)	0.23 [0.16, 0.30]	0.34 [0.28, 0.39]
MiSight	Autorefraction spherical equivalent (D)	-0.27 [-0.41, -0.12]	-0.37 [-0.52, -0.23]
	Axial length (mm)	0.10 [0.03, 0.17]	0.15 [0.09, 0.21]
Between-group difference	Autorefraction spherical equivalent (D)	0.38 [0.21, 0.55]	0.42 [0.22, 0.63]
	Axial length (mm)	-0.13 [-0.21, -0.05]	-0.19 [-0.27, -0.11]

Adjusted mean [95% confidence interval (CI)]

PMDA's view:
The MIST401 (Part 1) study demonstrated the efficacy of MiSight in patients with myopia. In view of the following points, the foreign clinical data can be extrapolated to Japanese patients.

- Although the rates of myopia progression have been reported to differ between Japanese and non-Japanese patients, myopia progression in childhood due to axial elongation has been confirmed to be in common between Japan and overseas.

- There is no clear difference in the diagnosis of and treatment algorithm for myopia between Japan and overseas.
- There were no clear differences in the changes from baseline to 1 year in cycloplegic autorefraction spherical equivalent and axial length between the MIST401 (Part 1) and MIST-J studies (Table 32).

6.B.(3) Safety

The applicant's explanation about the safety of MiSight:

In view of the following results of the MIST401 (Part 1) and MIST401 (Part 2) studies, MiSight is considered to have no safety problem:

- There were no clear differences in adverse events for which a causal relationship to the test device could not be ruled out in the MIST401 (Part 1) study between the MiSight and control groups, and they were all non-serious adverse events and confirmed to have resolved. The adverse events for which a causal relationship to the test device could not be ruled out in the MIST401 (Part 2) study resolved, except for corneal ulcer and scar in 1 patient and scar in 1 patient. The corrected visual acuity in the one patient with corneal ulcer and scar and another patient with scar was a decimal visual acuity of ≥1.0. These events did not result in study discontinuation.
- There were no malfunction-related injuries.
- There were no slit lamp microscopy findings of Grade >1 resulting in the study discontinuation, and all of the findings resolved.
- The proportions of patients who responded "Annoying" or "Very annoying" for the subjective symptoms (ghost images [double images], halos [luminous ring], and glare [dazzle]) related to visual disorders during use of MiSight were 6.3% (4 of 64 patients) in the MiSight group and 2.9% (2 of 68 patients) in the control group in the MIST401 (Part 1) study, and 4.0% (2 of 50 patients) in the T6 group and 0% (0 of 50 patients) in the T3 group in the MIST401 (Part 2) study. In addition, the proportion of such patients in the MIST-J study was 16.7% in the control group. Considering these results, there were no clear differences between the MiSight and control groups.
- No clear differences in the autorefraction spherical equivalent during fixation to each visual distance were observed between the MiSight and control groups at baseline as well as at 1, 2, and 3 years of lens wear.

In view of the following results of the MIST-J study, MiSight is considered to have no safety problem in Japanese patients. To promote the proper use of MiSight, the applicant plans to disseminate information on MiSight and make users aware of the proper use by providing training seminars, etc.

- Adverse events for which a causal relationship to the test device could not be ruled out occurred in 3.3% (1 of 30) of patients in the MiSight group only, and they were confirmed to have resolved.
- There were no malfunction-related injuries.
- Slit lamp microscopy findings of Grade ≥2 occurred in 1 eye in the MiSight group, which was only Grade 2 "Other (hordeolum)." Its causal relationship to the test device was ruled out.
- The cytology of corneal endothelial cells showed no clear changes in the mean values of corneal endothelial cell density, coefficient of variation, and incidence of hexagonal cells from the screening to 1 year of the lens use in both groups.
- A questionnaire survey on the subjective symptoms (ghost images [double images], halos [luminous ring], and glare [dazzle]) related to visual disorders during use of MiSight was conducted. The results

showed that the proportion of the patients who responded “Annoying” or “Very annoying” was 16.7% (5 of 30 patients) in both groups.

- No clear differences in the autorefraction spherical equivalent during fixation to each visual distance were observed between the MiSight and control groups at 1 month as well as at 1 year.

PMDA’s view:
Based on the submitted clinical data and the applicant’s explanation, no significant concerns about the safety of MiSight were identified in patients with myopia; therefore, the safety of MiSight is acceptable.

However, MiSight is a medical device to slow the progression of myopia and mainly intended for use in children. Although no safety problems were identified in clinical studies, MiSight should be used in the actual clinical practice under the appropriate supervision and management by a physician. As described in Section “6.B.(5) Duration of use of MiSight,” patients may wear MiSight lenses for a long period of time, and therefore the progression of myopia and the occurrence of ophthalmic complications should be monitored periodically to ensure the risk-benefit balance of MiSight. Since children may have difficulty in self-management, their parents or legal guardian should be fully informed of MiSight so that their child can adhere to the proper use.

Based on the above, PMDA concluded that the approval condition described later should be imposed so that MiSight should be sold exclusively to patients who are confirmed to use the device under the appropriate supervision and management by a physician, and that not only materials for healthcare professionals but also materials for patients and their parents or legal guardian should prepared.

6.B.(4) Clinical positioning and intended use or indications

PMDA asked the applicant to explain the clinical positioning of MiSight, how to separate the use of MiSight from the approved myopia progression control treatment, and reasons why “patients aged ≥8 years with myopic ametropia potentially leading to axial elongation” were selected as the intended patients for the intended use or indications.

The applicant’s explanation:
Because (i) the submitted clinical data demonstrated the efficacy of MiSight in slowing the progression of myopia and (ii) no significant safety problems were identified, MiSight could be positioned as one of treatment options for slowing the progression of myopia. In Japan, “Ryjusea Mini Ophthalmic Solution 0.025%” is approved as a drug for slowing the progression of myopia, but no data from clinical studies evaluating the efficacy and safety of MiSight versus the drug were available. Therefore, how to use these products separately based on their efficacy is currently unknown. An appropriate product should be selected according to the safety profile of each product, patients’ capacity to wear and remove contact lenses, and other conditions.

In addition, the intended use or indications of MiSight were defined as “correction of visual acuity and slowing the progression of myopia in patients aged ≥8 years with myopic ametropia potentially leading to axial elongation” for the following reasons:

- The MIST401 (Part 1) and MIST-J studies included patients who were aged 8 to 12 years at enrollment. However, published literature reported that although the mean age at myopia stabilization was 15.6 years, the age at which myopia stabilized differed individually; myopia stabilized by the age of 15, 18, 21, and 24 years in 48%, 77%, 90%, and 96% of participants, respectively.[16] Based on the above findings, it is considered difficult to specify an upper limit of the age. However, the lower limit of the age was set at "≥8 years" because safe use of contact lenses by patients aged ≥8 years was demonstrated in clinical studies, although MiSight is expected to slow myopia progression in patients aged <8 years who are in the process of axial elongation.
- The MIST401 (Part 1) and MIST-J studies included patients who had autorefraction spherical equivalent ranging from −0.75 to −4.00 D at enrollment. However, in view of the following points, there is little need to limit the intended patient population of MiSight according to myopia levels.
  - The mean autorefraction spherical equivalent at the age of 8 to 12 years ranges from −0.25 to −1.49 D. A fact-finding survey on myopia in school children conducted in 2023 by the Ministry of Education, Culture, Sports, Science and Technology[17] reported that there were children with myopia of >−4.00 D, which was outside the range of myopia levels specified for the clinical studies.
  - The treatment zone of MiSight is considered [redacted].

PMDA asked the applicant to explain, based on the clinical data, whether the efficacy of MiSight differs depending on the patient's age and myopia level. PMDA also asked the applicant to explain the basis for selecting the range of vertex power of [redacted] D for regulatory submission, although the vertex power of MiSight ranged from −0.75 to −6.0 D in the clinical studies.

The applicant's explanation:
Tables 33, 34, 35, and 36 show the results of subgroup analyses of the primary endpoint by baseline characteristics of patients in the MIST401 (Part 1) and MIST-J studies. Since MiSight demonstrated superior efficacy over the control in all subgroups, the efficacy is unlikely to differ clearly depending on the age and myopia level in patients with myopia progression. Lenses with vertex power which were not used in the clinical studies can also be expected to be effective for the following and other reasons: The efficacy was demonstrated consistently regardless of myopia level, the treatment zone of MiSight is [redacted], and the creation of myopic defocus was confirmed [redacted].

Table 33. Changes from baseline to 3 years in cycloplegic autorefraction spherical equivalent (D) by characteristics
(MIST401 [Part 1] study)

Characteristics		Treatment group	Number of eyes	Change from baseline	Between-group difference
All		Control	112	-1.31 [-1.46, -1.16]	0.67 [0.49, 0.84]
		MiSight	104	-0.65 [-0.79, -0.50]	
Age	≤10 years	Control	62	-1.34 [-1.49, -1.18]	0.71 [0.49, 0.92]
		MiSight	60	-0.63 [-0.78, -0.47]	
	≥11 years	Control	50	-1.09 [-1.26, -0.92]	0.70 [0.45, 0.95]
		MiSight	44	-0.39 [-0.57, -0.21]	
Autorefraction spherical equivalent	<-2.00 D	Control	53	-1.12 [-1.28, -0.95]	0.59 [0.36, 0.82]
		MiSight	57	-0.52 [-0.68, -0.37]	
	≥-2.00 D	Control	59	-1.31 [-1.47, -1.16]	0.84 [0.61, 1.07]
		MiSight	47	-0.47 [-0.64, -0.29]	

Adjusted mean [95% CI]

Table 34. Changes from baseline to 3 years in axial length (mm) by characteristics
(MIST401 [Part 1] study)

Characteristics		Treatment group	Number of eyes	Change from baseline	Between-group difference
All		Control	112	0.62 [0.56, 0.69]	-0.28 [-0.36, -0.20]
		MiSight	104	0.34 [0.27, 0.41]	
Age	≤10 years	Control	62	0.70 [0.63, 0.77]	-0.34 [-0.44, -0.24]
		MiSight	60	0.36 [0.29, 0.43]	
	≥11 years	Control	50	0.52 [0.44, 0.60]	-0.30 [-0.41, -0.18]
		MiSight	44	0.23 [0.14, 0.31]	
Autorefraction spherical equivalent	<-2.00 D	Control	53	0.57 [0.49, 0.64]	-0.26 [-0.37, -0.16]
		MiSight	57	0.31 [0.23, 0.38]	
	≥-2.00 D	Control	59	0.65 [0.58, 0.73]	-0.38 [-0.49, -0.27]
		MiSight	47	0.27 [0.19, 0.35]	

Adjusted mean [95% CI]

Table 35. Changes from baseline to 1 year in cycloplegic autorefraction spherical equivalent (D) by characteristics
(MIST-J study)

Characteristics		Treatment group	Number of eyes	Change from baseline	Between-group difference
All		Control	60	-0.79 [-0.94, -0.65]	0.42 [0.22, 0.63]
		MiSight	58	-0.37 [-0.52, -0.23]	
Age	≤10 years	Control	30	-0.94 [-1.17, -0.71]	0.39 [0.07, 0.71]
		MiSight	32	-0.55 [-0.77, -0.33]	
	≥11 years	Control	30	-0.65 [-0.85, -0.46]	0.48 [0.19, 0.77]
		MiSight	26	-0.17 [-0.38, 0.033]	
Autorefraction spherical equivalent	<-2.00 D	Control	22	-0.64 [-0.82, -0.45]	0.38 [0.14, 0.62]
		MiSight	31	-0.26 [-0.42, -0.11]	
	≥-2.00 D	Control	38	-0.87 [-1.07, -0.67]	0.40 [0.09, 0.71]
		MiSight	27	-0.47 [-0.71, -0.24]	

Adjusted mean [95% CI]

Table 36. Changes from baseline to 1 year in axial length (mm) by characteristics (MIST-J study)

Characteristics		Treatment group	Number of eyes	Change from baseline	Between-group difference
All		Control	60	0.34 [0.28, 0.39]	-0.19 [-0.27, -0.11]
		MiSight	58	0.15 [0.09, 0.21]	
Age	≤10 years	Control	30	0.42 [0.32, 0.52]	-0.21 [-0.35, -0.08]
		MiSight	32	0.21 [0.11, 0.30]	
	≥11 years	Control	30	0.25 [0.19, 0.31]	-0.15 [-0.23, -0.06]
		MiSight	26	0.10 [0.04, 0.16]	
Autorefraction spherical equivalent	<-2.00 D	Control	22	0.26 [0.18, 0.34]	-0.14 [-0.25, -0.04]
		MiSight	31	0.12 [0.05, 0.19]	
	≥-2.00 D	Control	38	0.36 [0.29, 0.44]	-0.17 [-0.28, -0.07]
		MiSight	27	0.19 [0.11, 0.27]	

Adjusted mean [95% CI]

PMDA's view:

The applicant's explanation is understandable taking into account that "Ryjusea Mini Ophthalmic Solution 0.025%" was recently approved in Japan. In the future, however, the applicant should appropriately provide information to healthcare professionals in cooperation with relevant academic societies, as necessary, when new findings on how to separate the use of MiSight from other myopia progression control treatments and on the possibility of combination of those become available.

Based on the applicant's explanation and the following points, PMDA concluded that the Intended Use or Indications of MiSight should be modified appropriately from "Vision correction and slowing the progression of myopia in patients aged ≥8 years with myopic ametropia potentially leading to axial elongation" to "Vision correction and slowing the progression of myopia."

- It is obvious that "eyes with myopic ametropia" require vision correction and slowing the progression of myopia, and therefore the phrase should be deleted.
- No clear criteria for "(myopic ametropia) potentially leading to axial elongation" are currently available. Therefore, this phrase should be deleted from the Intended Us or Indications section and added to the Precautions Concerning the Intended Use or Indications section in Information on precautions, etc. to state that eligible patients should be selected with reference to data evaluated in clinical studies, such as patient age and refractive status.
- Patients aged ≥8 years were enrolled in the clinical studies from the viewpoint of efficacy evaluation and prevention of dropout. However, MiSight is expected to have efficacy even in patients aged <8 years if they are able to adhere to the proper use with the help of their parents or legal guardian. Therefore, the definition of the lower age limit is unnecessary in the Intended Use or Indications section if Information on precautions, etc. includes a cautionary statement that eligible patients should be selected with reference to the age of patients evaluated in the clinical studies.
- The applicant's explanation about the range of vertex power is understandable, and the range of [redacted] to [redacted] D is acceptable, based on the comments raised in the Expert Discussion. The definition of the vertex power is unnecessary in the Intended Use section if the range is specified in the Shape, Structure, and Principle section, and if the spherical equivalent power of the patients evaluated in the clinical studies is provided in Information on precautions, etc.

In addition, based on the comments raised in the Expert Discussion, PMDA has concluded that since it is known that children may experience pseudomyopia due to tension of the ciliary muscle or other causes,

a physician should differentiate myopia from other eye illness such as pseudomyopia and amblyopia in the diagnosis of myopia. Further, it is necessary to confirm, before the start of the MiSight lens wear, that myopia is appropriately diagnosed and that the patient is eligible for the treatment.

Based on the above, PMDA concluded that the following cautionary statements should be included in Information on precautions, etc.:

- Eligbible patients should be selected with reference to information on the patients enrolled in the clinical studies, such as patient age and myopia status [No clinical studies have been conducted in patients aged <8 years or patients aged ≥13 years]. In addition, since children may have difficulty in self-management, eligible patients should be selected in consideration of the patient age and ability to adhere to the proper use.
- MiSight should be used in patients diagnosed with myopia by appropriately conducting cycloplegic refraction.
- Physicians should confirm the eligibility of the patient for use of MiSight by ascertaining that the patient has no complications of eye illness such as amblyopia which should be treated with a higher priority and is not classified as having refractive myopia (e.g., keratoconus, abnormal corneal shape, spherophakia)

6.B.(5) Duration of use of MiSight

PMDA asked the applicant to explain the duration of use of MiSight.

The applicant's explanation:

In view of the following points, the applicant considers that physicians should perform periodical examinations in patients who started the use of MiSight and determine whether the continued use of MiSight is appropriate for each patient while checking the status of myopia progression, etc.

- Discontinuation of the therapeutic intervention should be determined in consideration of the patient's age and ocular growth pattern. It is difficult to establish uniform criteria for determining the duration of use and necessity of continued use of MiSight.
- However, myopia progression reportedly tends to slow commonly in late teenage years.[18] Therefore, if changes in refraction and axial length are controlled and myopia stabilization is confirmed in patients who have reached their late teens, then such findings may be deemed as a guide for discontinuation of the MiSight lens wear.
- Discontinuation of lens wear should be considered if there is a risk of injury to the eye health due to a problem with the method of using the lens, or if the lens cannot be worn according to the specified schedule due to any life cycle change.

PMDA's view:

The applicant's explanations are understandable. However, since MiSight is intended to slow the progression of myopia, its efficacy may not be expected in patients with stabilized myopia progression. The treatment with MiSight may be prolonged, but unnecessarily prolonged use should be avoided. Thus, cautionary statements should be included in Information on precautions, etc. so that the appropriateness of continued use of MiSight can be determined after performing periodic examinations to check the status of myopia progression and the occurrence of ocular complications.

6.B.(6) Myopia progression due to discontinuation of the MiSight lens wear

To allow patients to be benefited from the treatment for slowing myopia progression, the therapeutic effect of MiSight needs to continue after discontinuation of the treatment. Reportedly, myopia progression was accelerated in foreign clinical studies of other treatments for slowing myopia progression after discontinuation.[19,20] Based on the findings, PMDA asked the applicant to explain myopia progression after discontinuation of the MiSight lens wear.

The applicant's explanation:

Based on the following results, etc. in the MIST402 study, the myopia progression after discontinuation of the MiSight lens wear is unlikely to be a clinically issue:

- The changes in cycloplegic autorefraction spherical equivalent and axial length in the MIST402 study were lower than those in the control group of the MIST401 (Part 1) study (annualized value).
- In the MIST402 study, the mean age at baseline was 16.2 years, and the change in axial length from baseline (annualized value) was 0.10 mm. Given that the annual axial elongation in patients aged 14 years with progressive myopia is predicted to be 0.12 mm,[21] the change in the axial length in the MIST402 study is inferred to be similar to the change predicted from the age.
- If rapid myopia progression is observed after discontinuation of the MiSight lens wear, the degree of progression may depend on the duration of the MiSight lens wear. However, in the MIST402 study, there was no clear difference in the degree of myopia progression between the T3 and T6 groups in which the patients wore the MiSight lens for 3 and 6 years, respectively.

PMDA's view:

No data on comparison of myopia progression after discontinuation of lens wear between the MiSight and control groups are available, and there is a limitation in comparing the annualized axial elongation reported in the results of the MIST402 study and published literature. Since no clear difference in myopia progression before and after discontinuation of lens wear was observed in the T6 group in the MIST402 study, the applicant's explanation that the progression of myopia after discontinuation of lens wear is unlikely to be a clinical issue is understandable to some extent. However, cautionary statements should be established to ensure that examination is periodically performed to check myopia progression even after discontinuation of the MiSight lens wear.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant explained that post-marketing surveillance, etc. were considered unnecessary because (i) MiSight has sufficient clinical performance overseas with no safety problems; and (ii) "Proclear 1 Day," of which the raw materials, method of use, etc. are same as those of MiSight, has sufficient clinical performance with no safety problems in Japan.

7.B Outline of the review conducted by PMDA

PMDA's view:

In addition to the applicant's explanation, the submitted clinical data demonstrated the efficacy of MiSight, with no specific safety concerns identified. Based on the comments raised in the Expert Discussion, designation of the use-results evaluation is unnecessary.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

PMDA's review of the application for MiSight primarily focused on the efficacy and safety of MiSight. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion.

In the MIST401 (Part 1) study, the efficacy and safety of MiSight were evaluated in patients with myopia. Cycloplegic autorefraction spherical equivalent and axial length selected as the primary endpoints demonstrated the superiority of MiSight over the control. The safety of MiSight was also shown to be clinically tolerable on the assumption that appropriate cautionary statements is established. The results of the MIST-J study were consistent with those of the MIST401 (Part 1) study, showing the extrapolability of clinical data of the MIST401 (Part 1) study to Japanese patients. The progression of myopia after discontinuation of the MiSight lens wear was investigated in the MIST402 study and confirmed to be not clinically problematic.

Since MiSight is mainly intended for use in children, appropriate supervision and management by a physician are required for its use. Periodic examinations should be performed to monitor the status of myopia progression and the occurrence of complications, and the risk-benefit balance of MiSight should be evaluated before use. Based on the above, PMDA considers that the inclusion of precautions in Information on precautions, etc. and provision of sufficient information through materials as well as establishment of a system for use under appropriate supervision and management by physicians are very important. To this end, PMDA instructed the applicant to include cautionary statements described in the Section "6.B Outline of the review conducted by PMDA" in Information on precautions, etc. with the approval condition described below. The applicant accepted it.

Based on the results above, PMDA has concluded that MiSight may be approved for the following intended use.

Intended Use

Vision correction and slowing the progression of myopia

Approval Condition

The applicant is required to take necessary measures to ensure that the product is used appropriately only in eligible patients under the supervision of physicians with adequate knowledge and experience.

The product is not classified as a biological product or a specified biological product.

PMDA has concluded that the present application should be deliberated by the Committee on Medical Devices and *In-vitro* Diagnostics.

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