PROTOCOL

VERSION 1

MiSight® Lens Wear Cessation Study

SPONSOR:	CooperVision Inc.
STUDY NUMBER:	MIST-402
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DOCUMENT CHANGE HISTORY

Revision	Originator	Description of Change(s)	Date
1.0	[redacted]	Original protocol	11 June 2018

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AL	Axial Length
CFR	Code of Federal Regulations
CRF	Case Report Form
CL	Contact lens
CRO	Contract Research Organisation
D	Dioptre
EDC	Electronic data Capture
eCRF	Electronic CRF
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IOL	Intra Ocular Lens
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISO	International Standards Organisation
MK	Microbial Keratitis
mm	Millimetre
NIH	US National Institutes of Health
PD	Pupillary Distance
SD	Standard Deviation
SEALs	Superior Epithelial Arcuate Lesion
SERE	Spherical Equivalent Refractive Error
SOP	Standard Operating Procedure
US	United States
VA	Visual acuity

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MIST-402

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PERSONNEL AND FACILITIES

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MiSight® Lens Wear Cessation Study

MIST-402

SYNOPSIS

STUDY OBJECTIVES: To quantify the effect of ceasing MiSight treatment after 3 or 6 years' use.

STUDY DESIGN: This will be a bilateral, open label, dispensing study with approximately 90 MiSight subjects refit to Proclear 1-day lens for 1 year.

RANDOMISATION: All subjects will be refit to Proclear 1 Day. As such, no randomization will take place.

MASKING: There will be no masking for this study.

TEST PRODUCTS: Lenses to be worn are shown below:

Brand	Proclear 1 Day
Manufacturer	CooperVision
Material/ water content	omafilcon A / 62%
Design	Single vision
Base curve (mm)	8.70
Diameter (mm)	14.2
Sphere powers (D)	-0.25 to -8.00 (0.50D steps after -6.00D)

LENS CARE PRODUCTS: These are daily disposable lenses and, therefore, contact lens cleaning, soaking and disinfecting products should not be required

Rewetting/comfort drops given to the subject by the investigator may be used in this study as needed to lubricate and rewet lenses.

STUDY POPULATION: Approximately 90 existing MiSight (CL) wearers will be enrolled in the study:

Inclusion Criteria:

- Successfully completed the CVI08008 (MIST-401)- Part 2 study
- Visual acuity (VA) with CLs better than +0.25 log MAR (>6/12 or >20/40) in both eyes
- No ocular pathology or other contraindication to contact lens wear.
- Where applicable (dependent on local requirements), have:
    - read the Informed Assent
    - been given an explanation of the Informed Assent,
    - indicated an understanding of the Informed Assent and
    - signed the Informed Assent Form.

  Or
    - read the Informed Consent,
    - been given an explanation of the Informed Consent,
    - indicated an understanding of the Informed Consent and
    - signed the Informed Consent Form.
- Where applicable (dependent on local requirements), have their parent or legal guardian:

  - read the Informed Consent,
  - been given an explanation of the Informed Consent,
  - indicated an understanding of the Informed Consent and
  - signed the Informed Consent Form.
- Along with their parent or guardian (if applicable), be capable of comprehending the nature of the study, and be willing and able to adhere to the instructions set forth in this protocol.
- Along with their parent or guardian (if applicable), agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study (see Visit Schedule, Section 7.2.1).
- Agree to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the study and to inform the study investigator if this schedule is interrupted. (Wearing time may be modified by the study staff for health reasons.)
- Be in good general health, based on his/her and parent's/guardian's (if applicable) knowledge.
- Have best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25 Snellen equivalent) or better in each eye.

Exclusion Criteria:

- Regular use of ocular medications (prescription or over-the-counter).
- Current use of systemic medications which may significantly affect contact lens wear, tear film production, pupil size, accommodation or refractive state.
- Pregnant or lactating or planning a pregnancy at the time of enrolment.
- Known ocular or systemic disease such as, but not limited to: anterior uveitis or iritis, episcleritis or scleritis, glaucoma, Sjogren's syndrome, lupus erythematosus, scleroderma, or diabetes.
- Any ocular, systemic or neuro-developmental conditions that could influence refractive development.
- Keratoconus or an irregular cornea.
- Biomicroscope findings that would contraindicate contact lens wear including, but not limited to:
  - Any active anterior segment ocular disease that would contraindicate contact lens wear.
  - clinically significant (Grade 3 or 4) abnormalities of the anterior segment, lids, conjunctiva, sclera or associated structures.
- The investigator for any reason considers that it is not in the best interest of the subject to participate in the study.

NO. SITES: Four sites (UK, Portugal, Singapore and Canada).

END-POINTS:

Efficacy End-points

Primary:

- Change in spherical equivalent refractive error (SERE)
- Change in axial length (AL)

Safety End-points

As the study lens is approved in Europe (CE marked) as well as Canada and Singapore, no safety end points are required. Safety will be

monitored through routine biomicroscopy and reporting of adverse events.

STUDY VISITS: There will be a maximum of four scheduled visits

Visit 1: Baseline / Trial Fit / Lens Dispensing
Visit 2: 2-week Follow Up (Optional)* (14 days ± 5 days from dispensing)
Visit 3: 6-month Follow Up (180 days ± 14 days from dispensing)
Visit 4: 12-month Follow Up and Exit (360 days ± 44 days from dispensing)

* This is an optional visit if, in the investigator's opinion, it is needed to confirm adaptation to the new lenses.

STUDY VARIABLES: **Key Variables**:

Cycloplegic refraction (Seiko WR5100K) – Baseline, 6 & 12-months

Axial length (Zeiss IOL Master)

Other Variables:

1 INTRODUCTION

The three-year pivotal study (MIST-401; CVI08008) noted a significant reduction in myopic progression and axial growth with MiSight in comparison with a single vision control.[1]

Myopia progression studies with atropine eyedrop treatment have noted what appeared to be an acceleration of progression when the treatment with atropine was ceased. During the 12-months after cessation, with 1% concentration the average rate of myopia progression was greater than that shown by a control group.[2] Subsequent studies by the same group studied both the efficacy and post study acceleration following treatment and then cessation of lower concentrations of atropine (0.01%, 0.1%, 0.5%). These concentrations showed a dose dependent post-treatment acceleration compared to the 1% concentration.[3]

There is only one published study involving soft contact lenses with positive spherical aberration that has investigated myopia progression following cessation of treatment. This study found no evidence of a rebound effect after ceasing treatment.[4]

The purpose of this study will be to investigate the effect of ceasing treatment with MiSight contact lenses.

In MIST-401, subjects were randomly assigned to one of two groups: the test group wore MiSight contact lenses while the control group wore Proclear 1 Day lenses. After completion of this 3-year pivotal study ("Part 1"), all subjects were offered the opportunity to enrol for an additional three-year study, all wearing MiSight lenses (MIST-401 Part 2).

Subjects who have completed the MIST-401 MiSight study (Part 1 and Part 2) will be invited to enrol on this 1-year follow-on study (MIST-402). Thus, subjects entering the study will have worn MiSight lenses for either 3 or 6 years.

2 STUDY OBJECTIVES

The aim of this study will be to determine the rate of myopic progression following cessation of wear of MiSight contact lenses.

Specifically,

i. To quantify spherical equivalent refractive error (SERE) progression following cessation of 3 or 6 years' use of MiSight contact lenses.

ii. To quantify axial length (AL) progression following cessation of 3 or 6 years' use of MiSight contact lenses.

3 STUDY DESIGN & RATIONALE

3.1 Study Design

This will be a bilateral, open label, dispensing study with approximately 90 subjects currently wearing MiSight lenses refit to Proclear 1-day lenses for one year.

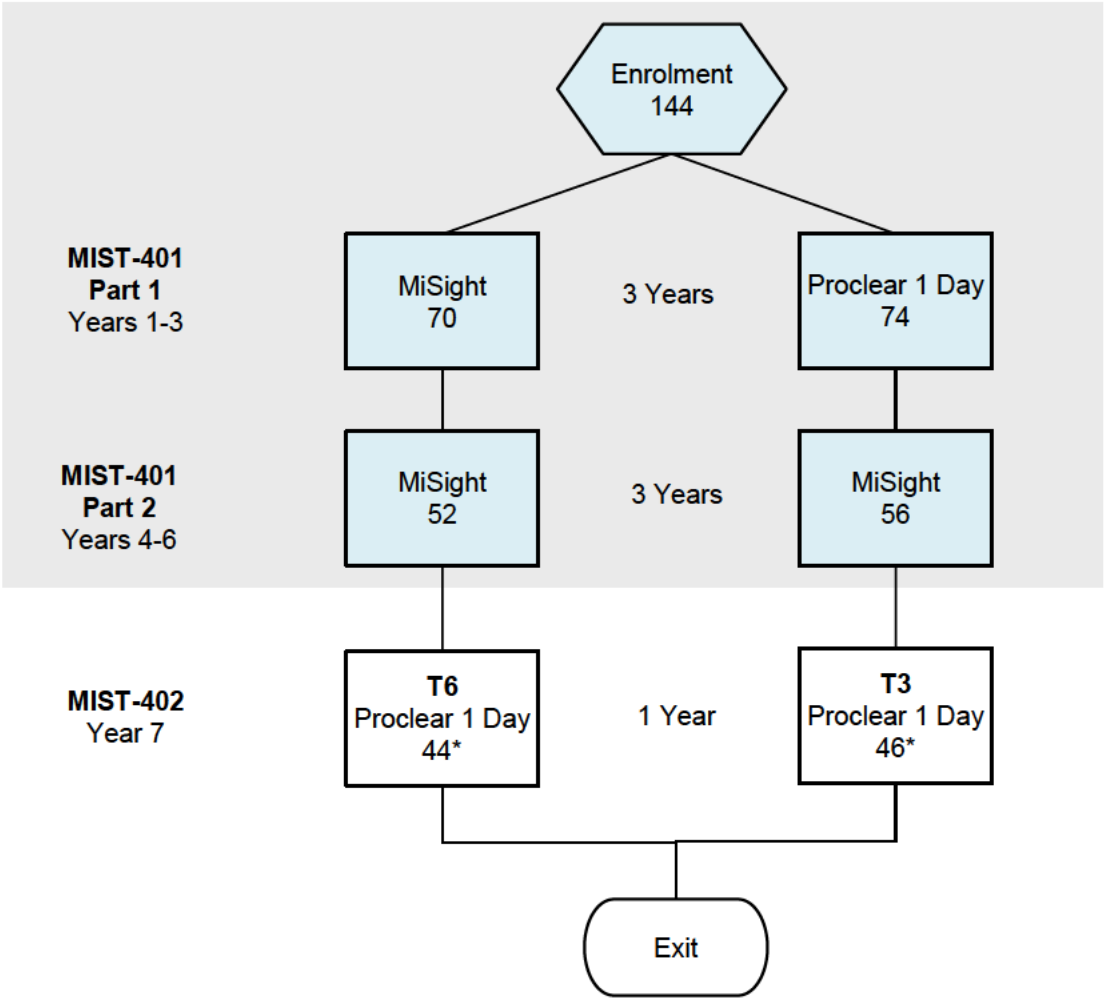
Subjects who have completed MIST-401 – Parts 1 and 2 will be invited to participate in the study.

Thus, there will be two groups of subjects, as described earlier and shown in the following diagram:

Group T6: 6 years of MiSight wear – refit to Proclear 1 Day

Group T3: 3 years of MiSight wear – refit to Proclear 1 Day

Figure 1: Flowchart of subject contact lens experience - Enrolment
(Grey area indicates enrolment numbers for previous study MIST-401 – Parts 1 and 2)



* Estimated based on current status of MIST 401- Part 2

3.2 Study Rationale

Since there is no defined level of myopia progression that would constitute a classification of 'acceleration' or 'rebound', the primary and secondary hypotheses are targeted primarily on quantifying any change in myopia progression rate (SERE and AL) in these post treatment groups.

The primary outcome analysis will compare the rate of myopia progression after cessation of MiSight wear to the average rate of myopia progression found in the Control group (Proclear 1-Day) in the 3-year MIST-401 - Part 1 study. The myopia progression rate should not be more than this progression rate found with standard contact lens usage.

The secondary outcome analysis will compare a subject's rate of myopia progression after cessation of MiSight wear to their average rate of myopia progression with MiSight lenses for the immediately previous three years in the MIST-401-Part 2 study. Because MiSight lenses have demonstrated a myopia control effect, we might expect a slightly increased rate of myopia progression when wearing regular lenses.

[redacted]

3.3 Primary Outcome Hypothesis

i. The mean myopic progression (Δ SERE) after cessation of MiSight wear will be non-inferior to (i.e. not greater than) the mean annual myopic progression of the Control group in MIST-401-Part 1.

ii. The mean myopic progression (Δ AL) after cessation of MiSight wear will be non-inferior to (i.e. not greater than) the mean annual myopic progression of the Control group in MIST-401-(Part 1).

A non-inferiority margin of 0.25D or 0.1mm will be used for SERE and AL respectively.

3.4 Secondary Outcome Hypotheses

i. The mean myopic progression (Δ SERE) after cessation of MiSight wear will be greater than the mean annual myopic progression for the immediately previous 3 year's MiSight treatment (MIST-401-Part 2).

ii. The mean myopic progression (Δ AL) after cessation of MiSight wear will be greater than the mean annual myopic progression for the immediately previous 3 year's MiSight treatment (MIST-401-Part 2).

3.5 Tertiary Outcome Hypotheses

i. [redacted].

ii. [redacted]

[redacted]

3.6 Safety Hypothesis

The study lenses are approved in all the countries where the study is taking place, therefore, no safety end points are required.

However, in order to ensure the continued safety of the subjects in the trial, slit lamp findings will be assessed at all visits and the entrance spectacle refraction and VA will be collected at the start and end of the study. Adverse events will also be recorded and monitored following the procedures listed in Section 8.

3.7 Masking

There will be no masking for this study.

3.8 Randomisation

All subjects will be refit to Proclear 1 Day, as such no randomization will take place.

4 STUDY POPULATION

4.1 Number of Sites

There are four investigational sites (UK, Portugal, Singapore and Canada)

4.2 Investigator Recruitment

The investigators will be those that have already taken part in the MIST-401 study Parts 1 and 2).

For the MIST-401 study the study sites were colleges of optometry. Study sites were selected based on the experience of the site investigator and staff in conducting clinical trials, the availability of potential study subjects, and the interest of the site in performing the trial.

4.3 Number of Subjects

Approximately 90 existing soft contact lens wearers who have successfully completed the MIST-401 Parts 1 and 2 study will be enrolled.

Each subject will be required to attend up to four scheduled study visits over a period of approximately 12 months.

The study population has been chosen as they have already completed either 3 or 6 years of wear in MiSight contact lenses

4.4 Inclusion Criteria

All subjects must satisfy the following conditions prior to inclusion in the study:

i. Successfully completed the CVI08008 (MIST-401) Parts 1 and 2

ii. Visual acuity (VA) with CLs better than +0.25 log MAR (>6/12 or >20/40) in both eyes

iii. No ocular pathology or other contraindication to contact lens wear

iv. Where applicable (dependent on local requirements), have:

   a. read the Informed Assent

   b. been given an explanation of the Informed Assent,

   c. indicated an understanding of the Informed Assent and

   d. signed the Informed Assent Form.

   Or

   e. read the Informed Consent,

   f. been given an explanation of the Informed Consent,

   g. indicated an understanding of the Informed Consent and

   h. signed the Informed Consent Form.

v. Where applicable (dependent on local requirements), have their parent or legal guardian:

   a. read the Informed Consent,

   b. been given an explanation of the Informed Consent,

   c. indicated an understanding of the Informed Consent and

d. signed the Informed Consent Form.

vi. Along with their parent or guardian (if applicable), be capable of comprehending the nature of the study, and be willing and able to adhere to the instructions set forth in this protocol.

vii. Along with their parent or guardian (if applicable), agree to maintain the visit schedule and be able to keep all appointments as specified in the study protocol for the duration of the study (see Visit Schedule, Section 7.2.1).

viii. Agree to wear the assigned contact lenses for a minimum of 10 hours per day, at least 6 days per week, for the duration of the study and to inform the study investigator if this schedule is interrupted. (Wearing time may be modified by the study staff for health reasons.)

ix. Be in good general health, based on his/her and parent's/guardian's (if applicable) knowledge.

x. Have best-corrected visual acuity by manifest refraction of +0.10 logMAR (20/25 Snellen equivalent) or better in each eye.

4.5 Exclusion Criteria

Any of the following will render a subject ineligible for inclusion:

i. Regular use of ocular medications (prescription or over-the-counter).

ii. Current use of systemic medications which, in the investigators opinion, may significantly affect contact lens wear, tear film production, pupil size, accommodation or refractive state.

iii. Pregnant or lactating or planning a pregnancy at the time of enrolment.

iv. Known ocular or systemic disease such as, but not limited to: anterior uveitis or iritis, episcleritis or scleritis, glaucoma, Sjogren's syndrome, lupus erythematosus, scleroderma, or diabetes.

v. Any ocular, systemic or neuro-developmental conditions that in the investigators opinion, could influence refractive development.

vi. Keratoconus or an irregular cornea.

vii. Biomicroscope findings that would contraindicate contact lens wear including, but not limited to:

a. Any active anterior segment ocular disease that would contraindicate contact lens wear.

b. clinically significant (Grade 3 or 4) abnormalities of the anterior segment, lids, conjunctiva, sclera or associated structures.

viii. The investigator for any reason considers that it is not in the best interest of the subject to participate in the study.

4.6 Subject Identification

Subjects will be identified by a four-digit code made up of the site number and their enrolment number.

As data will be compared back to the MIST-401 Parts 1 and 2 data, the sites and subjects will keep the same number as they had in that study. Therefore, the subject numbers will not be sequential as subject numbers that were discontinued in the previous study, will not be used in this study.

4.7 Study Withdrawal Criteria

Due to the nature of the study, no circumstances are foreseen whereby this study would be prematurely terminated. However, if during the study it becomes evident to either the sponsor or VCR that the study contact lenses pose a threat to subject well-being, the study will be terminated and the Research Ethics Committee (REC) will be advised of the reason for termination.

4.8 Subject Replacement

Subjects that are discontinued or drop out of the study will not be replaced.

4.9 Medications/Treatments Permitted and Not Permitted During the Study

Preservative free rewetting/comfort drops may be used in this study as needed to lubricate and rewet lenses, if agreed by the investigator.

The use of topical ocular medications is contraindicated at all times during this study unless prescribed as part of a treatment for an adverse event. The use of any ocular medications to treat conditions that arise will require temporary suspension of lens wear, an adverse event report, and evaluation of the subject for discontinuation from the study.

For any adverse event where lens wear is suspended, an unscheduled follow-up evaluation of the subject must be performed before allowing the subject to return to lens wear. Subjects may not return to lens wear until all topical ocular medications have been discontinued and a documented exam has verified the resolution of the adverse event.

4.9.1 Concomitant Medications

Changes in concomitant medications from those recorded at the initial visit should be indicated on the follow-up visit forms by checking ‘Yes’ on the concomitant medication question and recording the change in the appropriate EDC forms.

4.10 Procedures for Monitoring Subject Adherence

To track compliance, subjects will be asked their average contact lens wearing times, average number of days lenses are worn per week and about their contact lens experience at each follow-up visit. This will be in the form of a questionnaire given to the subjects or questions on the CRF.

5 MATERIALS

5.1 Study Lenses

Table 1: Lens Details

Brand	Proclear 1 Day
Manufacturer	CooperVision
Material/ water content	omafilcon A / 62%
Design	Single vision
Base curve (mm)	8.70
Diameter (mm)	14.2
Sphere powers (D)	-0.25D to -8.00D (0.50D steps after -6.00D)

Only lenses distributed by VCR may be used for the study.

If additional lenses are required, investigators should contact VCR.

5.2 Lens Care Products and Other Study Products

Subjects will be instructed to dispose of their contact lenses every night and insert a new pair of lenses in the morning; therefore, contact lens cleaning, soaking and disinfecting products should not be required. If the contact lenses must be removed briefly during the day for swimming or other activities then the subject should throw the lenses away and replace with a new pair afterwards. Subjects should always carry a spare pair of contact lenses and spectacles in case the contact lenses need to be removed for any reason when not at home.

Rewetting/comfort drops given to the subject by the investigator may be used in this study as needed to lubricate and rewet lenses.

5.3 Product Accountability

The applicable study initiation documents (including but not limited to: investigator agreement, Statement of Investigator, IRB/IEC approval, protocol signature document, financial disclosure form, etc.) must be received by the CRO before investigational materials can be shipped to the investigational site. If applicable, approval from the appropriate regulatory authorities must be obtained before shipping lenses to the investigational site.

All study lenses will be sent to the investigational site by the CRO (see page 6). An initial bank of lenses will be sent to the investigational site for initial dispensing.

All study lenses must be inventoried upon receipt, recorded on the Lens Accountability Form by the investigational site and stored in a secure area, segregated from any other materials, and issued only as directed in the protocol. The investigational site must document the dispensing and return (unused lenses only) of each investigational lens for each subject using the Lens Dispensing Forms provided in each subject's study record.

Study sites will not be required to retain any packaging from used lenses.

Study subjects must discontinue wearing the study lenses at the exit visit and all used lenses must be discarded. All unused lenses must be returned to the study site and recorded on the subject's Lens Dispensing Form. All unused lenses must be returned at the 12-month visit.

Study product accountability will be checked by the study monitor (assigned by the sponsor or CRO) during site monitoring. All unused lenses, returned from subjects or never dispensed to the study subjects, must be available to the study monitor for verification of lens accountability at the completion of the study. Any discrepancies in study lens accountability must be explained by the investigator. After the study monitor has verified product accountability, any unused materials will be returned to the CRO or the sponsor at the end of the study unless the investigator is otherwise directed by the CRO or the study sponsor. All product returned to the CRO or sponsor will be documented on the Lens Accountability Form.

5.4 Lens Wearing Schedule

Subjects should be instructed to wear the study lenses for at least 6 days per week and preferably for 7 days per week. Subjects should wear the lenses for a minimum of 10 hours per day.

Subject who do not wear for the minimum time will not be discontinued from the study but the data may be analysed separately.

5.5 Potential Risks and Benefits for Human Subjects

Potential Risks and benefits for human subjects wearing contact lenses are summarised in the Informed consent document (separate document).

5.6 Study Documents and eCRFs

The following forms will be completed where appropriate:

eCRFs:

A) Baseline forms (including eligibility checklist)
B) Trial Fit / Dispensing form
C) Follow-up forms (including Unscheduled Visit)
D) Adverse Event forms
E) Study Exit forms

[redacted]

Additional Forms

A) Patient Information Sheet/Statement of Informed Consent
B) Participant Information Guide
C) Enrolment Log
D) Product Accountability Log
E) Dispensing Log
F) Source Document Record Labels

6 TREATMENT

6.1 Study Product Formulations

The test lenses will be shipped in blister packs containing a buffered saline packaging solution. The labelling of lenses and packaging will be the standard packaging which will indicate lens power, base curve, diameter, lot number and expiration date.

6.2 Lens Administration

Lenses will be used on a daily disposable wear basis. Subjects should be instructed to wear the study lenses for at least 6 days per week and preferably for 7 days per week. Subjects should wear the lenses for a minimum of 10 hours per day.

7 METHODS AND ASSESSMENTS

7.1 Subject Recruitment

Subjects on the MIST-401 Part 2 study will be sent a letter inviting them to take part in this study.

The procedures listed below will be conducted on all subjects. Variables must be collected in the order they are listed on the eCRF.

7.2 Study Visits

7.2.1 Visit Schedule

There will be a maximum of four scheduled visits as follows:

Visit 1:	Baseline / Trial Fit / Lens Dispensing
Visit 2:	2-week Follow Up (Optional)* (14 days ± 5 days from dispensing)
Visit 3:	6-month Follow Up (180 days ± 14 days from dispensing)
Visit 4:	12-month Follow Up and Exit (360 days ± 44 days from Dispensing)

* This is an optional visit if, in the investigator's opinion, it is needed to confirm adaptation to the new lenses

A Visit Schedule will be supplied to all sites and will list the visit windows; this can assist in the scheduling of visits within the appropriate window.

The Investigator should confirm with the subject that they are able to attend the follow-up visit within the visit window before enrolling them in the study. If, in extreme situations (sickness, unforeseen circumstances), the subject can only attend outside the visit window, the Investigator should discuss with VCR whether this visit can be considered a scheduled visit.

A scheduled follow-up visit may only take place when the subject attends wearing the study lenses. If this is not the case and the subject is not experiencing any problems with the lenses, the appointment will be re-scheduled, ideally within the visit window.

See Section 7.5 for instructions regarding unscheduled visits.

7.2.2 Visit 1: Enrolment/ Screening /Baseline

The subjects will complete Visit 1 after exiting the MIST-401 Part 2 study. This may be on a different day from the MIST-401-Part 2 study exit, however they should only wear spectacles in between exiting the MIST-401-Part 2 study and entering this study. If this is more than 1-week from the MIST-401-Part 2 study exit then all assessments in the table below will need to be repeated.

Prior to being evaluated, the subject and his/her parent/guardian (if applicable) must have the study explained to them; read or have the informed assent and consent documents read to them and indicate understanding of the documents.

The consent and assent documents will be provided to subjects and their parent/guardians as applicable. The content of the consent and assent documents may vary slightly from country to country, based on the requirements of the respective IRB/IEC. The investigator must ensure that they use only the consent form which has been approved by both the sponsor and the IRB/IEC/Health Authority (if appropriate).

The investigator or designee will explain the study purpose, procedures, and subject responsibilities to the potential subject and his/her parent/guardian (if applicable). The subject's willingness and ability to fulfil the study's requirements will be determined.

If the subject agrees to participate in the study, written informed consent will be obtained from the subject and/or parent or guardian (if applicable). Where the subject is under the country's age where they are able to sign the consent form themselves, written informed assent will be obtained from the subject. The assent and consent forms will be signed and dated in the presence of the investigator's staff after opportunity has been given for discussion, questions or concerns by the subject and his or her parent/guardian (if applicable).

The investigator and the person who explained the informed consent and assent (if applicable) must also sign the documents. The original documents will be retained in the subject's records, and copies will be provided to the subject and parent/guardian (if applicable).

A subject is considered enrolled when the Statement of Informed Consent / Assent documents (where applicable) have been fully executed. The subject will then be added to the enrolment log.

All subjects enrolled should be accounted for, even if they are not dispensed lenses. After enrolment, a subject is considered active and should be accounted for at every visit until the completion of, or discontinuation from the study.

Some baseline data for MIST-402 may include measurements already collected at the final visit for MIST-401 Part 2 (see table below). These measurements do not need to be repeated and the information can be taken from that final visit CRF as long as within a week from enrollment in MIST-402.

The following Screening/Baseline procedures will be conducted on all subjects once enrolled i.e. after the consent/assent (where applicable) documents have been fully executed:

Number	Assessment	Procedure	Instructions and gradings
1	Subject Demographics	Record age, sex and ethnicity	

Number	Assessment	Procedure	Instructions and gradings
2	Medical History	Record medications and associated medical history (such as allergies etc)	
3	Previous Study Lens Wearing Time*	Record the typical insertion & removal times, number of hours worn today, number of days worn per week.	Appendix A – Subjective Assessments
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	
6	Entrance Distance VA	Record the Monocular high contrast distance VA with habitual correction	Appendix A - Visual Acuity and Refraction
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
10	Manifest Subjective Refraction*	Record the subject's manifest refraction, recording all cylinder in the minus cylinder convention.	Appendix A - Visual Acuity and Refraction
11	BCDVA*	With the manifest refraction record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]

Number	Assessment	Procedure	Instructions and gradings
14	Cycloplegia (only if not taking the information from MIST-401 study)	Induce Cycloplegia according to the instructions provided and wait for 25 minutes before conducting cycloplegic assessments.	Appendix A - Cycloplegia
15	[redacted]	[redacted]	[redacted]
16	Cycloplegic Auto Refraction*	For the auto-refraction measurements the average of the 5 measurements should be recorded on the eCRF after eliminating sphere or cylinder readings that are more than 1.00D from the mode.	Appendix A - Visual Acuity and Refraction
17	Axial Length*	For the axial length measurements, the average of the 5 measurements should be recorded on the eCRF.	Appendix A - Ocular Characteristics
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	Eligibility	Confirm if subject is eligible and complete the eligibility criteria checklist. If at this point the subject is found to be ineligible, then complete an Exit eCRF and exit the subject from the study. The Investigator will also update the Enrolment Log and complete the Source Document Record – see Section 11.5 for further details	

* If already collected for the MIST-401 Part 2 study final visit, this measurement does not need to be repeated and the information can be taken from the final visit CRF as long as within a week of enrolment in MIST-402.

7.2.3 Visit 1: Trial Fit and Dispensing

If eligible, the subjects will undergo a trial fit in each eye with the lenses.

The following Trial Fit / Dispensing procedures will be conducted on eligible subjects:

Number	Assessment	Procedure	Instructions and gradings
1	Lens Parameters	Record the parameters of the lenses (lot number, lens powers). Lens type will be decided according to the randomisation log. Lens power will be based on non-cycloplegic subjective distance refraction	Appendix A – Lens Fit Assessment
2	Settling Time	Allow the lenses to settle for at least 10 minutes	
3	[redacted]	[redacted]	
4	DVA with CLs	With the contact lenses in record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
5	Spherical Over Refraction	With the contact lenses in record the spherical over refraction	Appendix A - Visual Acuity and Refraction
6	DVA with Over Refraction and CLs	With the contact lenses in and spherical over refraction record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
7	Suitability Review	If the subject was not able to achieve at least +0.10 logMAR, a second trial fit is allowed. Repeat procedures 1-8	
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	Dispensing Criteria	Lens fit and vision was acceptable	

Number	Assessment	Procedure	Instructions and gradings
13	Instructions	• The Participant Instruction Guide will be provided to all subjects and will give instructions regarding lens wear and care. • The Investigator or a clinical assistant will review instructions and warnings for lens wear, when to remove lenses, and other important issues with the participant. Participants who appear unable or unwilling to follow instructions to a degree that, in the Investigator's opinion, jeopardizes the participant's wellbeing or the validity of the study, will be discontinued. • Subject should be given enough lenses to last until the next visit. • Subject will be instructed to wear the lenses for at least 6 days per week and at least 10 hours per day	

7.2.4 Visit 2: 2-week Follow-Up (optional)

The 2-week follow-up visit will be scheduled 14 days (9-19 days) from the initial lens dispensing date.

This is an optional visit if, in the investigators opinion, it is needed to confirm adaptation to the new lenses. If the 2-week visit is being completed then the subject should wear the study lenses to the appointment.

The following clinical test variables will be recorded on the Follow-Up Visit eCRF:

Number	Assessment	Procedure	Instructions and gradings
1	Concomitant Medications and Medical History Review	Record any changes to concomitant medications or medical history and confirm if the changes are Adverse events	
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]

Number	Assessment	Procedure	Instructions and gradings
5	Entrance Distance VA	Record the Monocular high contrast distance VA with study contact lenses	Appendix A - Visual Acuity and Refraction
6	[redacted]	[redacted]	[redacted]
7	Spherical Over refraction	With the contact lenses in record the spherical over refraction	Appendix A - Visual Acuity and Refraction
8	DVA with CLs and Over refraction	With the contact lenses in and spherical over refraction record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	Instructions	• Subject should be given enough lenses to last until the next visit. • Subject will be instructed to wear the lenses for at least 6 days per week and at least 10 hours per day	

7.2.5 Visit 3: 6-month Follow-Up

The 6-month follow-up visit will be scheduled 6-months (166-194 days) from Visit 1. The subject should wear the study lenses to the appointment.

The following clinical test variables will be recorded on the Follow-Up Visit eCRF:

Number	Assessment	Procedure	Instructions and gradings
1	Concomitant Medications and Medical History Review	Record any changes to concomitant medications or medical history and confirm if the changes are Adverse events	
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	
6	Entrance Distance VA	Record the Monocular high contrast distance VA with study contact lenses	Appendix A - Visual Acuity and Refraction
7	[redacted]	[redacted]	[redacted]
8	Spherical Over Refraction	With the contact lenses in record the spherical over refraction	Appendix A - Visual Acuity and Refraction
9	DVA with CLs and Over Refraction	With the contact lenses in and spherical over refraction record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]

Number	Assessment	Procedure	Instructions and gradings
14	[redacted]	[redacted]	[redacted]
15	Cycloplegia	Induce Cycloplegia according to the instructions provided and wait for 25 minutes before conducting cycloplegic assessments.	Appendix A – Cycloplegia
16	[redacted]	[redacted]	[redacted]
17	Cycloplegic Auto Refraction	For the auto-refraction measurements the average of the 5 measurements should be recorded on the eCRF after eliminating sphere or cylinder readings that are more than 1.00D from the mode.	Appendix A - Visual Acuity and Refraction
18	Axial Length	For the axial length measurements, the average of the 5 measurements should be recorded on the eCRF.	Appendix A - Ocular Characteristics
19	[redacted]	[redacted]	[redacted]
20	Instructions	• Subject should be given enough lenses to last until the next visit. • Subject will be instructed to wear the lenses for at least 6 days per week and at least 10 hours per day	

7.2.6 Visit 4: 12-month Follow-Up

The 12-month follow-up visit will be scheduled 12-months (316-404 days) from Visit 1. The subject should wear the study lenses to the appointment.

The following clinical test variables will be recorded on the Follow-Up Visit eCRF:

Number	Assessment	Procedure	Instructions and gradings
1	Concomitant Medications and Medical History Review	Record any changes to concomitant medications or medical history and confirm if the changes are Adverse events	
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	
7	Entrance Distance VA	Record the Monocular high contrast distance VA with study contact lenses	Appendix A - Visual Acuity and Refraction
8	[redacted]	[redacted]	[redacted]
9	Spherical Over Refraction	With the contact lenses in record the spherical over refraction	Appendix A - Visual Acuity and Refraction
10	DVA with CLs and Over Refraction	With the contact lenses in and spherical over refraction record the best corrected distance VA	Appendix A - Visual Acuity and Refraction
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]

Number	Assessment	Procedure	Instructions and gradings
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
19	[redacted]	[redacted]	[redacted]
20	Cycloplegia	Induce Cycloplegia according to the instructions provided and wait for 25 minutes before conducting cycloplegic assessments.	Appendix A – Cycloplegia
21	[redacted]	[redacted]	[redacted]
22	Cycloplegic Auto Refraction	For the auto-refraction measurements the average of the 5 measurements should be recorded on the eCRF after eliminating sphere or cylinder readings that are more than 1.00D from the mode.	Appendix A - Visual Acuity and Refraction
23	Axial Length	For the axial length measurements, the average of the 5 measurements should be recorded on the eCRF.	Appendix A - Ocular Characteristics
24	[redacted]	[redacted]	[redacted]

Number	Assessment	Procedure	Instructions and gradings
25	[redacted]	[redacted]	[redacted]
26	Instructions	• Subject should be given enough lenses to last until the next visit. • Subject will be instructed to wear the lenses for at least 6 days per week and at least 10 hours per day • All unused study lenses will be collected from any subjects that were randomised to the Proclear 1-day contact lenses and retained at site until the Close out visit, unless otherwise instructed by VCR or the Sponsor	

7.2.7 Study Exit

The Study Exit eCRF must be completed when a subject exits the study. This will occur either at study completion, i.e. after Visit 4, or if the subject is discontinued from the study at another time. A Study Exit eCRF must be completed for all subjects who have a fully executed consent form. The exit date should also be recorded on the subjects named patient notes i.e. the Source Document Record. Post-study follow-up visits will be scheduled if the Investigator judges this is necessary. In this case the Exit eCRF will not be completed until all post-study visits have been completed.

At the study Exit Visit the following measurements are taken and recorded on the Exit eCRF:

Number	Assessment	Procedure	Instructions and gradings
1	Manifest Subjective Refraction	Record the subject's manifest refraction, recording all cylinder in the minus cylinder convention.	Appendix A - Visual Acuity and Refraction
2	BCDVA	If the VA at the Exit Visit is two or more lines worse than at Baseline, the Investigator will be required to provide an explanation and complete an adverse event eCRF	Appendix A - Visual Acuity and Refraction
3	[redacted]	[redacted]	[redacted]
4	Subject Study Exit	Record if the subject has successfully completed the study. If the subject is being exited due to discontinuation, further details need to be recorded on the exit form. This is described in Section 7.4.	

7.3 Clinical Variables

Table 2 summarises the clinical measurements to be taken at each visit.

The Baseline visit for MIST-402 is expected to be on the same day as MIST-401 Part 2 Exit Visit and will take place straight after the visit.

The MIST-402 Exit Visit will ordinarily take place immediately following Visit 4, but may take place earlier if a subject discontinues from the study. Slit lamp assessment to be performed if Exit Visit does not take place immediately after a follow-up visit.

Table 2: Summary of Clinical Measurements

PROCEDURES	BASELINE	DISPENSE	FOLLOW UP VISITS				
		Day 0	2 wk	6 Mo	12 Mo	UN-SCHED	Exit
Informed Consent and Assent	X						
Demographics	X						
Med History	X						
[redacted]	X*		X	X	X		
Concomitant medications review	X		X	X	X	X	
Lensometry	X*				X		
Entrance VA	X		X	X	X	X	
[redacted]		X	X	X	X		
[redacted]	X*						
[redacted]	X*				X		X+
[redacted]	X*				X		X+
[redacted]	X				X		
[redacted]	X		X	X	X	X	
[redacted]		X	X	X	X		
Contact lens over-refraction		X	X	X	X		
[redacted]		X	X	X	X		
[redacted]	X*			X	X		
Cycloplegic auto-refraction	X*			X	X		
Cycloplegic biometry (axial length)	X*			X	X		
[redacted]	X*				X		
[redacted]				X	X		
Exit VA			X	X	X		X+
Dispense study lenses		X	X	X			
Complications, Adverse Events &device malfunctions	Complete where applicable						
Parent/Guardian Informed Consent (if applicable)	X						
[redacted]	X						

* If already collected for the MIST-401 Part 2 study final visit, this measurement does not need to be repeated and the information can be taken from that final visit CRF as long as within a week of enrolment in MIST-402.
\+ if not completed at the associated visit.

7.4 Subject Discontinuation

Subjects may be discontinued from the study in the event of any of the following occurring:

i. Unacceptable subjective discomfort (i.e. lens cannot be tolerated or worn)

ii. Unacceptable slit lamp findings

iii. Unacceptable fit (i.e. lens too tight or too loose)

iv. At the discretion of the Investigator or the subject

v. Subject out of Rx range for the lenses.

In the event of discontinuation, the Study Exit eCRF must be completed and the study exit date recorded on the Source Document Record. The Investigator will indicate the primary reason for discontinuation by selecting one of the boxes provided on the Exit eCRF. Comments can be added to the eCRF if necessary.

If a subject is discontinued outside of a visit window, an Unscheduled Visit eCRF must also be completed

7.5 Unscheduled Visits

An unscheduled visit is defined as any follow-up that occurs outside the visit window of the scheduled visit. A visit is also classified as unscheduled if the subject is seen a second time within the scheduled visit window.

Investigators should try as far as possible to schedule follow-up visits within the window. If this is not possible, and the visit falls outside the window, the visit will be an unscheduled visit, unless it has been agreed with VCR that it can be considered a scheduled visit.

Alternatively, the Investigator might judge that a follow-up visit is in the best interest of the subject and schedule two visits within the same window, e.g. follow-up of an adverse event. Unscheduled visits are also made available anytime at the subject's request.

Unscheduled visits will be recorded on the Unscheduled Visit eCRF. All variables listed on the forms must be completed unless the subject exhibits a condition that prohibits the completion of a full visit. If this is the case, a written explanation is required in the comments section (e.g. not wearing lenses due to discomfort).

Presenting VA and slit lamp variables must always be completed and the reason for the visit and any actions taken must be indicated on the forms.

7.6 Site Training and Visits

The study initiation will take place via on-line training modules and a phone call.

The sponsor or VCR may choose to initiate a site visit as deemed appropriate. If this occurs, VCR will email prior to the visit to arrange a convenient time. Interim and close-out monitoring visits will be documented in the Monitoring Plan which is a separate document.

8 ADVERSE EVENTS

An Adverse Event (AE) is defined as any unfavourable or unintended sign (including an abnormal finding), symptom or disease temporarily associated with the use of a study device whether or not related to the study device. All ocular AEs and related (to the study device and/or to the study procedures) non-ocular AEs, will be monitored and reported on throughout the study.

[redacted]

[redacted]

The Investigator will be required to judge whether or not an AE is device-related. Re-occurring device-related events from the same subject are usually tabulated as separate events. In the case where more than one diagnostic finding is associated with an AE, the event will be counted as one event and categorized under the most significant of the findings.

The Investigator will be required to report all AEs to the study CRO and also to their REC/IRB as required by the REC/IRB guidelines. The seriousness of an AE is categorized as being serious, significant, or non-significant (see Table 3).

Table 3: Adverse Events by Severity

Serious	Significant	Non-significant
Results in, or have the potential to cause either permanent impairment of a body function or damage to a body structure and may necessitate medical or surgical intervention. They include but are not limited to:	Symptomatic and warrant discontinuation of contact lens wear (temporary or permanent). They include but are not limited to:	Usually asymptomatic and do not warrant discontinuation of contact lens wear (temporary or permanent). However, as a precautionary measure the Investigator may decide to take action. They include but are not limited to:
MK – Microbial keratitis Permanent reduction in best spectacle-corrected visual acuity (≥ 2 lines) Central (4mm) corneal opacity Central corneal neovascularization Uveitis Iritis Endophthalmitis Hypopyon Hyphema Penetration of Bowman's membrane Persistent epithelial defect Limbal cell damage leading to conjunctivalisation Any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect	CLPU – Contact lens peripheral ulcer CLARE – Contact lens associated red eye SIE – Significant infiltrative event SEAL – Superior epithelial arcuate lesion Corneal warpage SLK – Superior limbic keratoconjunctivitis Other significant ≥grade 3 corneal findings (e.g. edema or abrasions) Any corneal event which necessitates lens wear discontinuation of > 2 weeks Non-CL related anterior segment events e.g. EKC – epidemic keratoconjunctivitis Temporary loss of ≥ 2 lines of best spectacle-corrected visual acuity New corneal scar without positive history	CLPC – Contact lens associated papillary conjunctivitis SPK – Superficial punctate keratitis Non-significant infiltrative event Blepharitis Meibomitis Contact dermatitis Localized allergic reactions, including solution-related ocular toxicity Conjunctivitis: Bacterial, Viral, Allergic Keratoconjunctivitis Any corneal event not explicitly defined as a serious or significant event which necessitates lens wear discontinuation <2 weeks Other slit lamp findings requiring treatment

For additional information, questions, or assistance in recording potential AEs, contact VCR.

8.1 Adverse Event Categorization

The Investigator will be required to rate the likelihood of an event being device-related (Possible, Probable, Highly Probable) or non-device-related (unlikely, definitely not) in their AE evaluation.

All device-related AEs will be tabulated and reported in the final report.

8.2 Adverse Event Reporting

On finding an AE the Investigator will complete an Adverse Event form (AE form) in EDC to capture the event.

The Investigator must notify Visioncare Research of the AE, so that they are able to provide advice and support to the Investigator on how to proceed.

The Investigator must do this by providing the information on the AE eCRF as soon as possible and no later than:

- 24 hours from discovery if event is Serious or Significant
- 5 working days from discovery if event is Non-Significant

Once the form is saved, an automatic email will be sent to VCR and the Sponsor to notify them of the event. If the AE form in EDC cannot be completed on the day of discovery of the AE, then the VCR monitor and the Sponsor (via email address [redacted]) must be contacted to notify them of the AE.

If applicable, VCR will advise the Investigator to notify the REC as per the REC requirements. VCR may notify the REC on behalf of the Investigator.

The Investigator must notify VCR in writing that the AE has been reported to the REC.

8.3 Adverse Event Documentation

Investigators are required to document and follow-up all AEs.

All AEs are documented on an AE form in EDC upon event discovery. For all ocular AEs, one AE form is used per eye. For AEs which are non-ocular but related to the study device or to the study procedures only one AE form needs to be completed in EDC per AE.

[redacted]

[redacted]

8.4 Adverse Event Follow-up

The Investigator will conduct follow-up examinations until the condition:

- Has returned to pre-event status,
- Is considered stabilized
- Or has been satisfactorily explained.

If the subject is referred for medical attention, they will be tracked by the Investigator until the aforementioned conditions are met.

Follow-up data will be collected on an unscheduled visit eCRF and on the AE form in EDC.

The Investigator should use his/her clinical judgement as to whether or not the subject reporting with an AE should continue in the study.

8.4.1 Device Malfunction

A malfunction means the failure of the device to meet its performance specification or otherwise perform as intended. A malfunction is considered reportable to the Sponsor if it would be likely to cause or contribute to a Serious Adverse Event.

The Investigator will be required to report all reportable device malfunctions to the study CRO/Sponsor via the applicable form in the EDC system.

8.4.2 Sponsor Safety Responsibilities

The sponsor will ensure that all participating Investigators are promptly informed of significant new safety information with respect to the study devices as per regulatory requirements.

To comply with this, the sponsor is responsible for promptly advising (in writing, via VCR) all Investigators conducting clinical studies of any incidents of serious or unexpected adverse events/unanticipated adverse device effects reported for the devices/products involved in those studies.

8.5 Study Completion

The study is completed when all subjects have completed visit 4 or been discontinued, and have been exited from the study.

9 DATA MANAGEMENT

9.1 Electronic Case Report Forms/Data Collection

The clinical data for this study will be entered by designated study site personnel onto electronic report forms (eCRFs) using the electronic data collection (EDC) system Medrio. Paper questionnaires will be given to subjects to complete.

Medrio is compliant with all relevant aspects of ICH/Good Clinical Practices and 21 CFR Part 11 (Electronic Records & Electronic Signatures) regulations.

9.2 Data Quality Assurance

When eCRFs are reviewed at VCR, they will be subjected to error checking and data queries will be raised electronically via the EDC system for resolution of omissions and discrepancies by the investigator.

Before the final closing of the database, the data will be checked and approved for analysis as per VCR SOPs. This includes checking for missing or erroneous data entries

9.3 Data Entry and Storage

All study data shall be entered into the study eCRFs. Completed subject questionnaires (paper) will be sent to VCR on a regular basis and data from the questionnaires will be hand entered into a database using DaCS software and then exported to an Excel database (Microsoft).

All statistical analyses will be completed by VCR using SAS software (SAS Institute Inc., Version 9.4 or later).

10 SAMPLE SIZE AND STATISTICAL METHODS

10.1 Sample Size Rationale

All eligible subjects that complete the MIST-401 Part 2 study will be invited to continue in this study. No new subjects will be enrolled. Based on the current study, there will be approximately 90 subjects completing the study: 44 with six years of MiSight experience (Group T6; original test group in Part 1) and 46 with three years of MiSight experience (Group T3; original control group in Part 1).

Primary Hypothesis

From the MIST-401 Part 1 study, the standard deviations for the paired mean difference and the 2-sample means were estimated. From these the sample sizes of 44 in group T6 and 46 in group T3 will provide at least 99% power to detect non-inferiority.

	Spherical Equivalent Refractive Error (D)		Axial Length (mm)	
Hypothesis	T3: Mean progression after 1-year cessation vs. "T3 Baseline" (Control group mean progression Y1-3)	T6: Mean progression after 1-year cessation vs. "T3 Baseline" (Control group mean progression Y1-3)	T3: Mean progression after 1-year cessation vs. "T3 Baseline" (Control group mean progression Y1-3)	T6: Mean progression after 1-year cessation vs. "T3 Baseline" (Control group mean progression Y1-3)
Test	Non-inferiority Paired (H_0: $\delta \leq$ NIM)	Non-inferiority 2-sample (H_0: $\delta \leq$ NIM)	Non-inferiority Paired (H_0: $\delta \leq$ NIM)	Non-inferiority 2-sample (H_0: $\delta \leq$ NIM)
Alpha	5% (1-sided)	5% (1-sided)	5% (1-sided)	5% (1-sided)
Sample Size	46	44	46	44
Expected Mean Difference	0.00D	0.00D	0.0 mm	0.0 mm
SD of mean or mean difference (σ)	0.36D	0.20D	0.10 mm	0.10 mm
Non-inferiority Margin (NIM)	0.25D	0.25D	0.1mm	0.1mm
Power	100%	100%	100%	99%

N.B. Calculations performed using Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

10.2 Primary End-points

The first primary outcome measure for progression of myopia is defined as the magnitude of change in the spherical equivalent refractive error. Cycloplegic autorefraction was selected to measure refractive error because of its accuracy, repeatability and objectivity, allowing for standardisation of measurements over time and within and across study centres. The spherocylindrical autorefractions will be recorded for each of 5 autorefraction measurements per eye after eliminating sphere or cylinder readings that are more than 1.00D from the mode, and the remaining readings averaged.

The second primary outcome measure is defined as the magnitude of change in axial length, as the progression of myopia has been shown to be associated with increases in axial length. Partial coherence interferometry will be used to measure axial length (mean of 5 readings) as it allows for non-contact measurements with better repeatability compared to conventional ultrasonography.

10.3 Statistical Considerations

All statistical analyses will be performed using the SAS software Version 9.4 or later (SAS Institute, Cary, NC). All data summaries will be performed using Microsoft Excel 2013 or later.

The final analysis will be completed after all subjects have been exited from the study, all queries have been resolved, and the database has been locked.

The mean annual myopic progression will be calculated by dividing the myopic progression for the years in question by the number of years for each subject.

The overall type I error rate will be preserved at 5%. The co-primary hypotheses will be simultaneously evaluated using α=0.05.

Data from unscheduled visits will not be included in the analysis.

10.4 Analysis Population

The statistical analysis for efficacy hypothesis testing will be performed as follows:

1. All available data – this will include all data from subjects that have completed follow-up visits. Counts of missing data will be included in the summary statistics.

2. Intent-to-treat – this will include any subject that has completed at least the 6-month visit. Missing data for 12-month myopia progression and axial length will be extrapolated, where possible, from the 6-month data for the intent-to-treat analysis.

10.5 Descriptive Statistics

Descriptive statistics will be reported at dispensing and each follow-up visit. Continuous variables will be summarized using mean, standard deviation, and range; and categorical data variables will be summarized using percent frequency distribution, mean, and SD. Nominal variables will be summarized using percentages.

Summaries will be presented by group (T3: 3 years of MiSight wear and T6: 6 years of MiSight wear.

10.6 Data Pooling

Data will be pooled from multiple study sites for this analysis, the basis for pooling comes from three factors:

- The study sites must implement one common protocol.
- The CRO must closely monitor study site protocol compliance.
- The study sites must use common data collection procedures.

10.7 Primary Statistical Analysis

T3 Group: The mean myopic progression after cessation of MiSight wear will be compared to the mean annual progression for the first three years (MIST-401 Part 1) for this same group of subjects (“T3 Baseline”) on a pairwise basis using linear mixed models. The model will include part, site, and the interaction of site-by-part as fixed effects and subject (nested in site) and eye as random effects. The fixed covariates: subject age group, sex, ethnicity, and baseline myopia (refractive error or axial length) may also be included. If there are convergence issues with the model some or all the covariates may be removed as required.

Statistical non-inferiority will be concluded if the 95% confidence limit of the mean difference of the progression rate after cessation compared to the T3 Baseline rate is greater than -0.25D/year for spherical equivalent refractive error or less than +0.1mm/year for axial length.

T6 Group: The mean myopic progression after cessation of MiSight wear will also be compared to the T3 Baseline mean annual progression using a linear mixed model. The model will include group (T6 or T3), site, and the interaction of site-by-group as fixed effects and subject (nested in site) and eye as random effects. The fixed covariates: subject age group, sex, ethnicity, and baseline myopia (refractive error or axial length) may also be included. If there are convergence issues with the model, some or all the covariates may be removed as required.

Statistical non-inferiority will be concluded if the 95% confidence limit of the mean difference of the progression rate after cessation compared to the T3 Baseline rate is greater than -0.25D/year for spherical equivalent refractive error or less than +0.1mm/year for axial length.

10.8 Secondary Statistical Analysis

The myopic progression after cessation of MiSight wear will be compared to the mean annual myopic progression for previous 3 year's MiSight treatment (MIST-401 – Part 2) on a pairwise basis using linear mixed models. The model will include treatment, site, years of MiSight wear (T6 or T3), and the interaction of site-by-treatment as fixed effects and subject (nested in site) and eye as random effects. The fixed covariates: subject age group, sex, ethnicity, and baseline myopia (refractive error or axial length) may also be included. If there are convergence issues with the model some or all the covariates may be removed as required.

A statistical difference will be concluded if the 95% confidence limit of the mean (test-control) difference is greater than 0 for spherical equivalent refractive error or less than 0 for axial length.

10.9 Tertiary Statistical Analysis

[redacted]

10.10 Additional Statistical Analysis

[redacted]

Any deviations from this analysis plan will be detailed in the study report.

10.11 Interim Analysis

There are no planned interim analyses for this study.

11 GENERAL STUDY MANAGEMENT

11.1 Relevant Standards

This protocol has been developed in accordance with the following:

- ISO 14155-1:2011 Clinical Investigation of Medical Devices for Human Subjects
- ISO 11980:2012 Contact Lenses and Contact Lens Care Products – Guidance for Clinical Investigations.
- ICH Harmonized Tripartite Guideline for Good Clinical Practice
- Declaration of Helsinki

The study will also be carried out in accordance with the VCR Quality Management System (ISO 9001:2015) and all the applicable local guidelines.

11.2 Ethics Review

The study protocol, Participant Information Sheet and Informed Consent Form, Informed Assent Form (where applicable) and all other required documents will be submitted to local REC/IRB for each site. A favourable opinion will be received prior to undertaking the study.

If significant protocol changes which require the preparation of an amendment are necessary, written REC/IRB approval will be obtained prior to implementation.

11.3 Protocol Deviations

The Investigators will not deviate from the protocol without written approval from the REC and VCR.

In medical emergencies, Investigators will use their judgement and remove the subject from immediate hazard. Any significant changes or deviations in the protocol will be the subject of a protocol amendment and must be pre-approved by the REC

If an unexpected deviation from the protocol occurs the Investigator must notify the CRO (VCR) immediately and the deviation from the protocol will be reported on a Protocol Deviation form in EDC and appropriate action taken.

11.4 Premature Termination of the Study

The sponsor reserves the right to terminate the study at any time for any reason including adverse effects. If it is determined that an unanticipated adverse device effect presents an unreasonable risk, then the entire investigation or part of the investigation presenting the risk shall be terminated as soon as possible. A written statement fully documenting the reasons for such termination will be provided to the REC.

11.5 Source Documentation

Unless otherwise documented, the eCRFs will be considered the source document. The sponsor or sponsor's representatives will be authorized to gain access to the source documentation for the purposes of monitoring and auditing the study (See Sections 11.6, 11.7).

The Source Document Record must be completed to comply with GCP guidelines. It is a permanent record within the patient's chart/notes that documents the subject's involvement in a clinical research study.

Contents of the source document record:

- Study number
- Subject ID
- Confirmation that subject met eligibility criteria
- Confirmation that subject signed the informed consent
- Confirmation that subject received a signed and dated copy of informed consent
- Date enrolled
- Details of lenses worn on study
- General notes
- Adverse events
- Reportable Protocol deviations
- Exit date
- Whether subject completed the study or discontinued
- Investigator's signature

The Source Document Record will be completed for each subject upon enrolment and then updated when required, e.g. when subject exits the study.

Note: If study information is collected using an automated piece of equipment, the information should be recorded directly from the instrument display to the eCRF or from an instrument printout if there is no display. The eCRF will become the source document if there is no printout. If a printout is obtained from the instrument, the original printout must be placed into the subject's study record as a source document with the subject number and date of recording noted on the printout.

11.6 Monitoring

Investigational site monitoring will be performed by a qualified study monitor identified by the sponsor or VCR. On-site visits will be completed at each site. The frequency and procedure of the monitoring visits will be documented in the Monitoring Plan which is in a separate document. The Investigator will allow the study monitor and sponsor representatives or REC to observe procedures and inspect study records and subjects' medical records throughout the study to verify protocol compliance, case report completeness, and investigational material accountability. Should the Investigator be found to be non-compliant and unwilling or unable to convert noncompliant practices, VCR in consultation with the sponsor will terminate the Investigator's role in the investigation and the REC will be notified.

11.7 Audits

The Investigator shall permit VCR, the sponsor and the REC to inspect its facilities, equipment, and study-related records, data and other documents upon reasonable notice. In addition, the REC may conduct such inspections as they deem necessary at any time whether or not advanced notice is given by them. The Investigator agrees to notify the sponsor or VCR within 24 hours (or as soon as reasonably practicable) of the start of any unannounced inspection by the REC or of the receipt from the REC of a notice of inspection whether given in writing or orally. If such notice is in writing, a copy with any attachments thereto shall be provided to VCR or the sponsor.

11.8 Records Retention

According to the ICH GCP guidelines the essential documents should be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The study lens material is already on the market and therefore the study documents should be kept for a minimum of two years after the end of the study. As the clinical research organisation supervising the study, VCR will also retain the written records for the same period of time. Following such retention period, the Investigator or the Clinical Site shall deliver to the sponsor all such Research Results, unless otherwise instructed in writing by the sponsor. Notwithstanding the foregoing, all information provided by or with respect to subjects in the Study will be furnished by Investigator and Clinical Site without patient names.

11.9 Confidentiality and Publication

This study is confidential in nature. The Investigator shall make no public statement, whether in written, oral or electronic form, relating to the CRO, the Sponsor, the substances, materials, products and devices being investigated or the Study itself without obtaining the prior written consent of the CRO or the Sponsor.

All information gathered during this study is proprietary and should be made available only to those directly involved in the study who have a need to know.

Authorised recipients of this data include:

- Investigator and co-investigator(s)
- Other allied health care personnel necessary for the conduct of the study
- IRB/IEC personnel
- Sponsor representatives
- Contract Research Organisation
- Designated study monitor
- Designated medical monitor
- FDA or other government regulatory agencies

All above personnel who are provided with data concerning this study will be informed of its confidential and proprietary nature. Release of this data (through presentation, publication or other written or oral communication) to other than the above listed personnel requires the prior written permission from the study Sponsor. Study investigators and all office personnel are prohibited from acknowledging participation in the study to individuals and organisations except those listed above. This includes sales representatives and other departments or subsidiaries of the sponsor without the direct written permission of the sponsor.

The study will conform to the requirements of the General Data Protection Regulation (GDPR). By signing the Informed Consent form the subject authorizes the sponsor and the sponsor's representatives (VCR) to access their optometric clinical records. The authorization will be indefinite; however, subjects will have the right to reverse this authorization at any time.

All patient information will have the patient name (or any information that can identify the patient apart from the mobile phone number) removed before leaving the Principal Investigator's site.

In accordance with the VCR Confidentiality Policy, the data, information, and reports arising from this project are the property of the sponsor company located in the USA. By signing the Informed Consent Form the subject also understands that their data will be sent to VCR [redacted]

[redacted] and the sponsor [redacted]. VCR will not release to a third party any information arising from this study unless required to do so by a legal or regulatory body. The electronic records will also be handled in accordance with the General Data Protection Regulation (GDPR) (2018). The Medrio EDC system is compliant with the U.S.-EU Safe Harbor Framework and the U.S.-Swiss Safe Harbor Framework as set forth by the U.S. Department of Commerce regarding the collection, use, and retention of personal information from European Union member countries and Switzerland. Medrio has certified that it adheres to the Safe Harbor Privacy Principles of notice, choice, onward transfer, security, data integrity, access, and enforcement to ensure the privacy of all information collected.

The trial results will be reported on the NIH website, www.ClinicalTrials.gov.

12 [redacted]

[redacted]

APPENDIX A

PROCEDURES, EQUIPMENT [redacted]

Detailed measurement procedures follow this Summary Table.

Variable	Equipment/Parameters	Procedure and [redacted] Measurement System
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Auto-refraction	Binocular Auto-refractor/ Keratometer WR-5100K or WAM-5500 (Grand Seiko) (D)	Measured using a Grand Seiko Auto Refractor, which is to be calibrated at the beginning of each measurement week. 5 measurements to be taken per eye.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted] **REFRACTION**		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

Variable	Equipment/Parameters	Procedure and [redacted] Measurement System
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Variable	Equipment/Parameters	Procedure and [redacted] Measurement System
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
CYCLOPLEGIA		
Cycloplegia	0.5% proparacaine or 0.4% benoxinate 1% tropicamide	1. Instil 1 drop of either 0.5% proparacaine **or** 0.4% benoxinate in the RE and LE. 2. One minute after instillation of the anaesthetic, instil 1 drop of 1% tropicamide in the RE and LE. Wait 5 minutes and instil another drop of 1% tropicamide in the RE and LE. 3. Wait 25 minutes before conducting cycloplegic assessments.
[redacted]		
[redacted]	[redacted]	[redacted]
Axial length	IOLMaster (Carl Zeiss) (mm)	With the subject fully cyclopleged, take 5 measurements of the RE and 5 measurements of the LE.
[redacted]		
[redacted]	[redacted]	[redacted]

Variable	Equipment/Parameters	Procedure and [redacted] Measurement System
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]		[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The following procedures apply to all auto-refraction measurements in the study (non-cycloplegic and cycloplegic):

Equipment

Binocular Auto Refractor/Keratometer WR-5100K or WAM-5500 (Grand Seiko)

Consult the Operating Manual for Proper Care of the Instrument, Preliminary Set-Up and more information on operating procedures.

Preparation

Important Considerations

The WR-5100K and WAM-5500 are precision optical instruments. Always handle with care especially when moving.

1. Ensure that the instrument is OFF before connecting to a power source. Connect instrument to safety power strip used for computers.
2. Do not touch the optical parts (i.e. mirrors or lenses) with fingers and be sure to avoid dust. When not in use, protect the instrument with a supplied dustproof cover and lock instrument down with anti-sliding screw lock.
3. If the instrument is not used for any length of time, disconnect the safety power strip, with the power cord, from the wall or floor outlet.

Calibration

At the beginning of EACH MEASUREMENT WEEK, check the calibration of the instrument and document on the instrument calibration / service record.

1. Set PD CENTRE to OFF and VD to 0 when measuring the supplied model eye.
2. When the measurement result of the model eye falls within the tolerance limits, proceed with the measurements. If the result exceeds the tolerance, contact CVI immediately and arrange for a Service Call for the instrument. Make a note on eCRF.

   TOLERANCE= +/-0.25 sph, +/-0.25 cyl, +/-0.03 Radius of curvature.
3. Set the model eye in the contact lens holder and be sure that it is level and centred relative to the optical axis of the instrument.
4. Proceed as you would for autorefraction of a real eye (see below).

Mode Selection Screen

1. Press the MODE switch on the right side of the LCD monitor

2. The following settings should be selected:

STEP	0.12
VD	0
CYL	-
START	QUICK(5)†
REF	NORMAL
KERATO	DIOPT
SE	OFF
PRINT FORM	ALL
DATA SCREEN	OFF
W-D (cm)	OFF
SCREEN ADJ	AS NEEDED
SAVE (min)	5
PD CENTRE	OFF
BUZZER	LOW
OPTION*	No.
DATE FORM	YMD
DATE	
TIME	

† Press '+' to change default setting from 3 to 5.

*This function allows you to input a message, set patients ID number, and download data to external computer

MESSAGE: Shifts to the screen for registering message. Enter your clinic's name the first time you use the WR-5100K or WAM 5500. After that it should print on all printouts.

No: Shifts to the screen for setting Subjects ID number. SET THIS FOR EACH NEW PATIENT.

Accom R/K Selection Switch: This switch is used to change the measurement mode.

The mode changes every time the switch is pressed as follows:

FAR → -2.0 D/50 cm → -2.5 D/40 cm → -3.0 D/33 cm → -4.0 D/2.5 cm→ -5.0 D/20 cm

R/K → R → K → FAR

Select R/K (refraction & keratometry)

Procedure

Patient Set Up

1. Check that there is sufficient printer paper in the printer and tissue paper on the chin rest. Follow manual instructions to replace.
2. Enter the Subject's ID using the OPTION mode above. For parent's auto-refraction, use Subject's ID and record 'father' or 'mother' on the printout.
3. Clean the chin rest, head rest and occluder with hydrogen peroxide or alcohol swab.
4. Establish the most comfortable and convenient position for the subject by vertically adjusting the instrument table to meet his/her eye level. Adjust chin rest until subject's outer canthus is aligned with the eye mark on the head rest.

Alignment

1. Use the joystick to image the subject's eye on the monitor.
2. A kerato ring will appear. (If the eyelid is over the illumination ring, ask the subject to open his/her eyes wider.)
3. Have subject view the appropriate target.

4. Align the reticule mark to the centre of the eye and focus on the subject's eye by moving the joystick forward or back.
5. An alignment mark (+) will appear.
6. Operate the joystick to bring the alignment mark (+) into the centre of the reticule mark.
7. It may be necessary to move the target to achieve alignment. When alignment is not achieved, values tend to fluctuate during measurement. If the subject moves his/her head during measurement, the AXIS value on the cyl reading will be in error.

Alignment Tips:

Move the fixation target in the opposite direction to how the reticule mark and reflected corneal image (ring image) are imaged relative to the pupil centre. Example, for the RE, if the reticule mark and kerato ring are on the left side of the subject's pupil, his/her gaze is too nasal. Thus, move the fixation point temporally. If difficulty with alignment occurs, examiner should place him or herself behind autorefractor and observe the brief flash of the measurement light, a faint red measurement pattern. Have a helper move the target until your eye is aligned with the centre of the pattern. Note location of the target. Minor adjustments will be needed for other subjects.

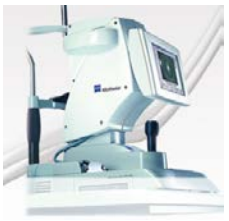
Measurement

Keeping the alignment mark (+) in the centre of the reticule mark, focus the subject's eye. This occurs when the kerato ring is thinnest.

1. Have the subject blink and regain fixation. Note: A blink ensures that tear residue or eye mucus trapped on the corneal surface does not cause measurement error.
2. Press the measurement start switch and record 5 measurements.
3. Move to the other eye and repeat the measurement procedure.

Note:

In the data analysis, potentially erroneous cylinder values or sphere values (identified as being greater than 1.0D from the mode), due to unsteady fixation, may be excluded.



Equipment

IOL Master (Carl Zeiss)

Preparation

1. Ensure that the child is not wearing contact lenses or spectacles.
2. Seat the child behind the IOL Master; adjust headrest, instrument and seat height to ensure comfort and to discourage unnecessary eye movements.
3. Enter the child's name, date of birth and study ID number.
4. Enter 'Overview Mode'. Adjust the instrument to measure the RE first. With the child viewing the yellow fixation light with the RE, adjust the instrument-to-eye distance until the six light reflections on the cornea are in focus. The small circle of lights and the cross-hairs should be centred in the child's pupil.

Procedure

1. Select ALM (Axial Length Measurement) mode. (In ALM mode, the fixation light turns to red.)
2. Ask the child whether they see the red fixation light clearly. If necessary, adjust the instrument until they do, and ask the child to keep looking at the fixation light.
3. Ask the child to blink before each measurement.
4. Take measurements of axial length by pressing the button on the joystick. The display next to the video image will show the measured axial length in millimetres (mm). The video image will be overlaid with a line graph similar to those from A-scan instruments. The signal-to-noise ratio (SNR) of the measuring signal will also be displayed. See 'Data Evaluation' section below for the significance of SNR.
5. After the second measurement, the mean of the axial length measurements will also be displayed. This value will be updated with each measurement. If the result of one measurement differs by more than 0.1 mm from the others, an 'Evaluation' message will be displayed in place of the mean value. This indicates that the results should be evaluated later (see 'Data Evaluation' section below).
6. 'Error' in the display field denotes readings with an SNR smaller than 1.6. These individual readings are excluded from the computation of the mean value, but they should not be deleted.
7. The number of measurements that have been taken on the eye on this particular day is displayed in the 'Mode' field of the status bar next to 'ALM'. If the count reaches 20, no further measurements of this eye can be taken on this day (date). This is for safety reasons. The counter cannot be reset and deleting readings does not affect the measurement counter.
8. Continue taking measures until 5 measurements of axial length have been made on the RE.
9. Do not delete any readings under any circumstances.
10. Re-align the instrument to measure the LE as described above for the RE.
11. Record 5 measurements of axial length of the LE.
12. Print out the Results. Check that the name of the child, their ID number and the date of measurement are correct on the printout.
13. Make at least one copy and store the paper version of the results in a master file.

Note: The IOLMaster is not intended as a data archive. The maximum length of time that data can be held on the IOLMaster is 100 days. The machine will then delete the data automatically.

Axial Length Data Evaluation

1. The signal to noise ratio (SNR) indicates the quality of measurement. Measurements with an SNR between 1.6 and 1.9 appear with an exclamation mark (!) after the measured value and the message 'Borderline value' will appear. 'Borderline value' does not necessarily mean that the reading must be rejected, but suggests that all axial length measurements for the eye should be checked for plausibility and consistency. If the 'uncertain' values are consistent with the other readings, the readings marked

'Borderline value' should be accepted as valid axial length measures. (In the DIMENZ trial we have only accepted data in which the SNR ≥ 2.0)

2. The hard-copy printout of the data will be used for verification in data audit. Although there is a backup facility on the IOLMaster, the saved files will only record the mean axial length, not each individual reading. Thus, print-out of the results is mandatory.

2. [redacted]

[redacted]

APPENDIX B

[redacted]