CooperVision™

Study Implementation document: Protocol

A DISPENSING CLINICAL TRIAL OF INVIGOR I LENS AGAINST CLARITI LENS

Sponsor Study Code:	CV-18-07
Version Number:	1.4
Document Date:	10 April 2018
Sponsor Company:	CooperVision, Inc.
Study Category:	[redacted]
Clinical Sites:	CORL, Indiana University CRC, University of California, Berkeley

Study Sponsor Representative: [redacted] Date: 10-April-2018

CooperVision Sponsor Manageme [redacted] Date: 10-APR-2018

Site Principal Investigator: _____ Date: _____
[redacted]

Site Principal Investigator: [redacted] Date: 10/APR/2018

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[redacted]

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[redacted]

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1 Introduction

CooperVision is evaluating the clinical performance of an investigational silicone-hydrogel lens referred to as the Invigor I (test) compared to the clariti lens (control) when worn on a daily wear basis over one-month for each lens type in a randomized, bilateral, cross-over, dispensing study.

[redacted]

2 Study Objective

This is a study to evaluate the clinical performance of the Invigor I lens when worn on a daily wear modality over one-month usage.

The primary variables of interest are:

- Lens surface wettability and surface deposits
- Lens fit performance

The secondary variable of interest is:

- Anterior ocular physiological response

[redacted]

[redacted]

[redacted]

3 Study Design

This will be a randomized, multicenter, bilateral, one month cross-over, double-masked, dispensing study comparing the Invigor I test lens against the clariti control lens. Each subject will be randomized to wear either the test or control as a matched pair first with a study duration of approximately two months. Both test and control lenses will be used in a daily wear modality for one month. There will be no planned lens replacement during the course of the one-month study unless due to lens damage/defects. It is anticipated that this study will involve up to 5 visits: Baseline (screening and dispense the first pair visit), 2-week follow-up visit for the first pair, one-month follow-up visit for the first pair and dispense the second pair, 2-week follow-up visit for the second pair, and one-month follow-up visit for the second pair and exit visit.

4 Ethics Review / Statement of Compliance

4.1 Relevant Standards / Guidelines

This implementation document has been developed in accordance with the following:

- ISO 14155 Clinical Investigation of Medical Devices for Human Subjects
- 21 CFR 812.2(b) Investigational Device Exemption – Abbreviated Requirements
- ISO 11980 Contact Lens and Lens Care products – Guidance for Clinical Investigations
- ICH Harmonized Tripartite Guideline for Good Clinical Practice
- Declaration of Helsinki

4.2 Institutional Review Board

This study will be conducted in accordance with Institutional Review Board regulations (U.S. 21CFR Part 56.103) or applicable IEC regulations. Copies of all IRB/IEC correspondence with the investigator/sponsor will be kept on file.

The conduct of this study will occur at two sites, CORL at Indiana University and CRC at the University of California, Berkeley. The conduct of this study will be approved for each site by an Institutional Review Board prior to commencement.

4.3 Informed Consent

Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is carried out.

5 Clinical Trial Registration

This Study will be registered with ClinicalTrials.gov in accordance with Section 801 of the Food and Drug Administration Act (FDAA) which mandates the registration of certain clinical trials of drugs and medical devices.

[redacted]

7 Materials and Methods

7.1 Subjects

This study will recruit at two clinical sites, the Clinical Optics Research Lab (CORL) at Indiana University and UC Berkeley Clinical Research Center (CRC). Up to 80 subjects will be dispensed across both sites with the aim of completing 60 subjects across both sites. Each subject will be given a unique ID number. Subject ID numbers will be assigned to the subjects sequentially and in ascending order, and will not be reused in the event of screen failure, subject dropout or discontinuation from the study.

Potential subjects will be identified from the investigators' clinic and research database records and/or will be actively recruited by advertisements circulated at the investigational sites as approved by the appropriate IRB.

There are no provisions for replacing subjects during the study who are discontinued from the study.

Additionally, all subjects must meet the study inclusion and exclusion criteria listed below.

Inclusion Criteria

A person is eligible for inclusion in the study if he/she:

- Has had a self-reported oculo-visual examination in the last two years.
- Is at least 18 years of age and has full legal capacity to volunteer.
- Has read and understood the information consent letter.
- Is willing and able to follow instructions and maintain the appointment schedule.
- Is correctable to a visual acuity of 20/40 or better (in each eye) with their habitual vision correction or 20/20 best-corrected.
- Currently wears soft contact lenses.
- Requires spectacle lens powers between -0.75 to -6.50 diopters sphere (0.25D steps).
- Has no more than 0.75 diopters of refractive astigmatism.
- Has clear corneas and no active ocular disease.
- Has not worn lenses for at least 12 hours before the examination.
- Has a usable pair of spectacle lenses if required for transportation to the site for the initial visit

Exclusion Criteria

A person will be excluded from the study if he/she:

- Has never worn contact lenses before.
- Has any systemic disease affecting ocular health.
- Is using any systemic or topical medications that will affect ocular health.
- Has any ocular pathology or severe insufficiency of lacrimal secretion (moderate to severe dry eyes) that would affect the wearing of contact lenses.
- Has persistent, clinically significant corneal or conjunctival staining using sodium fluorescein dye.
- Has any clinically significant lid or conjunctival abnormalities, active neovascularization or any central corneal scars.
- Is aphakic.
- Has undergone corneal refractive surgery.
- Is participating in any other type of eye related clinical or research study.
- Known allergy to a product used in this study (ex. Shellfish allergy)
- Is pregnant, lactating or planning a pregnancy at the time of enrolment (by verbal confirmation at the screening visit).

7.2 Number of Sites

The study will be take place at two sites: Indiana University School of Optometry within the Clinical Optics Research Lab (CORL) and UC Berkeley School of Optometry Clinical Research Center (CRC). These sites were selected based on the experience of their site investigators and staff in conducting clinical trials, the availability of potential study subjects, and the interest of the sites in performing the trial. A site investigator agreement and financial disclosure document will be in place prior to commencement of the trial.

[redacted]

7.3 Study Materials

7.3.1 Contact lens

Subjects will be randomized to receive either Test and Control lens as the first pair of contact lenses as per the randomization schedule. The lenses used in this study will be provided by the sponsor.

Both the Test and Control lenses will be labelled with "Investigational" wording on the labels for study masking purpose. The Test lens is an investigational product. It will be subject to preclinical assessment before being released for the study. The clariti contact lens material (somofilcon A) is FDA-cleared and is commercially available in the USA.

Details of the contact lenses are shown in Table 1.

Table 1: Study lenses

	Invigor I (Test)	clariti (Control)
Material	[redacted]	somofilcon A
Base Curve (mm)	8.6	8.6
Lens Diameter (mm)	14.2	14.2
Power (D)	-1.00 to -6.00 (0.25 steps)	-1.00 to -6.00 (0.25 steps)
Wear regimen	Daily wear	Daily wear

7.3.2 Contact Lens care

Subjects will be provided with an approved marketed lens care solution. The subject will be trained on how to use the care solution. The lens care products will be provided by the site.

7.3.3 Contact Lens Dispensing

The lenses will be inserted directly from the blister pack. The use of saline for rinsing prior to insertion is permitted if necessary. Saline will not be dispensed during the study. Subjects will not be allowed to use rewetting drops during the study.

7.3.4 Storage of Lenses and Lens Care Solutions

The study materials must be stored in a secure area and administered only by an unmasked study coordinator. It is recommended that all lenses and solutions be stored at controlled room temperature (59-86°F).

7.3.5 Clinical Supply Inventory

The investigator must keep an accurate accounting of the study product during the study. A detailed inventory must be completed for study supplies. The study supplies are to be used in accordance with the implementation document by subjects who are under the direct supervision of an investigator.

The subject will be issued with a pair of spare contact lenses in a sealed envelope to protect masking, along with the study supplies.

In the event that a lens in one eye needs to be replaced due to damage/defects before the one-month visit, only the damaged/defective lens will be replaced (e.g. not the lens in the other eye). A log of lens replacement will be recorded by the site. Subjects will be asked to keep and return the 'damaged/defective' lens.

7.3.6 Disposal of Consumables

This study dispenses consumables (lenses) to subject for use during the study. Study solutions used and/or study lenses worn by subject will be collected in lens cases stored in non-preserved saline solution and returned to the sponsor at the completion of the study. Leftover solution and cases will be disposed of either by the subject or by the clinical site staff. Lenses with product observations (e.g. moderate lens deposits), product defects, or product quality complaints will be collected and returned to the sponsor at the completion of the study.

7.3.7 Masking and Control of Study Materials

The contact lenses coding will be masked to both the investigator and subject.

Under normal circumstances, the mask will not be broken until all subjects have completed the study and the database is finalized. Otherwise, the mask should be broken only if a specific emergency treatment or course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may contact CVI in an emergency to request this information. In the event the mask is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unmasking must be documented.

7.3.8 Ordering and Accountability of Study Materials

The test and control lenses will be provided by the sponsor.

The investigator must complete an accurate accounting of the study product at the completion of the study. A detailed inventory must be completed for study supplies.

All unused and used materials will be returned to the sponsor at the end of the study unless the investigator is otherwise directed by the study sponsor.

7.4 Visit Schedule and Procedures

Prior to lens insertion biomicroscopy (including corneal and conjunctival staining) will be completed at the screening assessment. When possible, the screening will be combined with the baseline assessment. The investigator should confirm with the subject that they are able to attend the follow-up visits within the visit window before enrolling them in the study.

A scheduled follow-up visit of lens assessment/s 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 rescheduled, ideally within the visit window unless they are experiencing difficulty.

Visits that fall outside of the specified visit windows will be counted as unscheduled visits for analysis purposes. In addition to the screening visit, subjects will attend four visits (not including any unscheduled visits) and will wear the test or control lenses according to the study design.

There will be a minimum of five scheduled visits as follows:

Visit 1: Baseline/Screening/Dispensing Pair 1 (Day 0)
Visit 2: Two week follow up for Pair 1 (Day 14 ± 3)
Visit 3: One month follow up for Pair 1/Dispensing Pair 2 (Day 28 ± 4)
Visit 4: Two week follow up for Pair 2 (Day 14 ± 3)
Visit 5: One month follow up for Pair 2/Exit visit (Day 28 ± 4)

7.4.1 Visit 1: Screening / Baseline Visit / Dispensing Pair #1

Screening / Baseline

The following evaluations will be performed to assess eligibility according to the Inclusion and Exclusion Criteria at the Screening visit:

1. The subject is expected to attend the screening / baseline visit not wearing their habitual contact lens products for at least 12 hours prior to the study visit.
2. The subject will be required to read and sign an Informed Consent Form prior to enrolment. When the subject has signed the consent form, the subject will be considered to be enrolled on to the study.
3. Subject demographics and medical history (age, sex, race and ethnicity, medical conditions, medications, allergies) will be recorded by the investigator
4. Contact lens history (own lens information, rewetting drop use, and wear time)

5. Baseline monocular high illumination, high contrast (HIHC) entrance visual acuity with habitual spectacles or spectacle refraction
6. Auto refraction/auto keratometry: Flat and Steep K readings (D)
7. Sphero-cylindrical refraction (D), and best sphere refraction (D) & monocular & binocular distance visual acuity (HIHC) (logMAR)
8. The endpoint of this over refraction will be the best objective acuity, with (-) only being given with objective acuity, not subjective acuity improvement (not to the point that the letters start to shrink in size).

[redacted]

11. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales (Appendix 2).
12. The investigator will confirm that the subject meets the criteria set out in the inclusion criteria, and none of the exclusion criteria and is eligible to continue in the study.
13. The subject will be assigned a randomization ID and the first pair of contact lenses (either test or control) will be selected according to the randomization table.
14. Initial contact lens power chosen based on vertexed, spherical equivalent obtained from refraction. The contact lens power will be kept the same for both test and control.
15. The contact lenses will be dispensed by a research assistant / study coordinator / technician (in a manner which does not unmask the subject and investigator).

Dispensing Pair #1

1. The lenses will be inserted by the subject from the blister pack. The use of saline for rinsing prior to insertion is permitted if necessary.

[redacted]

3. The lens fit will be assessed for fit acceptance (acceptable or not acceptable) and absence of lens defects. If the fit is acceptable and there are no defects, the subject will be allowed to sit for 10 minutes to allow for the lenses to settle.
4. [redacted]

5 [redacted]

6 [redacted]

7. [redacted]

8. Monocular lens surface and fit will then be assessed and graded according to the CVI grading scales (Appendix 2):

   [redacted]

   c. Lens wettability (0-4 scale)

   [redacted]

   f. Lens deposition (0-4) and deposit type

   [redacted]

9. Monocular lens fit will be assessed and graded according to the CVI grading scales (Appendix 2). Lens fit will be video recorded in the event of poor fit.

   [redacted]

   b. Lens centration (optimal /slightly decentered, <0.5mm /extremely decentered >0.5mm, NTSI)

   [redacted]

[redacted]

i. Overall lens fit acceptance (0-4 scale, and yes/no) and investigator reason, if unacceptable.

[redacted]

10. The subject will be instructed to wear the study lenses for at least 8 hours per day, maximum of 16 hours per day and at least 5 days per week.
11. The subject will be dispensed with the lens care solution and instruction of use.
12. The subject will be given a pair of spare contact lenses.
13. The subject will be discharged and reminded to return for the 14-day visit of the first pair.

7.4.2 Visit 2: Two-week follow up of pair #1 (Day 14 ± 3)

*Subjects will be asked to wear lenses for **at least 2 hours** prior to the visit appointment.*

Subjects who attend without lenses in situ for at least two hours will be rescheduled.

The following procedures will be performed (any ocular measurement procedures outlined below will be carried out on each eye):

[redacted]

[redacted]

4. Monocular lens surface will then be assessed and graded according to CVI grading scales (Appendix 2).

[redacted]

c. Lens wettability (0-4 scale)

[redacted]

f. Lens deposition (0-4) and deposit type

[redacted]

5. Monocular lens fit will then be assessed and graded according to CVI grading scales (Appendix 2).

[redacted]

b. Lens centration (optimal /slightly decentered, <0.5mm /extremely decentered >0.5mm, NTSI)

[redacted]

i. Overall lens fit acceptance (0-4 scale, and yes/no) and investigator reason, if unacceptable.

[redacted]

7. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI grading scales. The same pair of contact lenses will be re-inserted.
8. The subject will be instructed to wear the study lenses for at least 8 hours per day, maximum of 16 hours per day and at least 5 days per week.
9. The subject will be discharged and reminded to return for the one-month visit.

7.4.3 Visit 3: One Month Visit Pair #1 (Day 28 ± 4)/Dispensing pair #2

*Subjects will be asked to wear lenses for **at least 2 hours** prior to the visit appointment.*

Subjects who attend without lenses in situ for at least two hours will be rescheduled.

The following procedures will be performed (any ocular measurement procedures outlined below will be carried out on each eye):

[redacted]

5. Monocular lens surface will then be assessed and graded according to CVI grading scales (Appendix 2).

[redacted]

c. Lens wettability (0-4 scale)

[redacted]

f. Lens deposition (0-4) and deposit type

[redacted]

[redacted]

6. Monocular lens fit will then be assessed and graded according to CVI grading scales (Appendix 2).

[redacted]

b. Lens centration (optimal /slightly decentered, <0.5mm /extremely decentered >0.5mm, NTSI)

[redacted]

i. Overall lens fit acceptance (0-4 scale, and yes/no) and investigator reason, if unacceptable.

[redacted]

8. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales.
9. There will be a 10-minute wash-out before insertion of pair 2.

Lens Dispensing Pair # 2

1. The second lens pair will be applied (according to the randomization table). The contact lenses will be provided by a study coordinator/technician to maintain masking of the investigator. The lenses will be inserted by the subject from the blister pack.
2. The use of saline for rinsing prior to insertion is permitted if necessary.
3. Lens powers of the second pair will be matched with the first pair if possible.

Procedures will be repeated as detailed in Visit 1 for pair 2 from section 7.4.1 (steps 1-13 in Dispensing pair#1 section).

7.4.4 Visit 4: Two-week follow up of pair #2 (Day 14 ± 3 of pair 2)

*Subjects will be asked to wear lenses for **at least 2 hours** prior to the visit appointment.*

Subjects who attend without lenses in situ for at least two hours will be rescheduled.

Procedures will be repeated as detailed from section 7.4.2 for pair 2 (steps 1-9).

7.4.5 Visit 5: One Month Visit Pair 2/Study Exit (Day 28 ± 4 of pair 2)

*Subjects will be asked to wear lenses for **at least 2 hours** prior to the visit appointment.*
Subjects who attend without lenses in situ for at least two hours will be rescheduled.

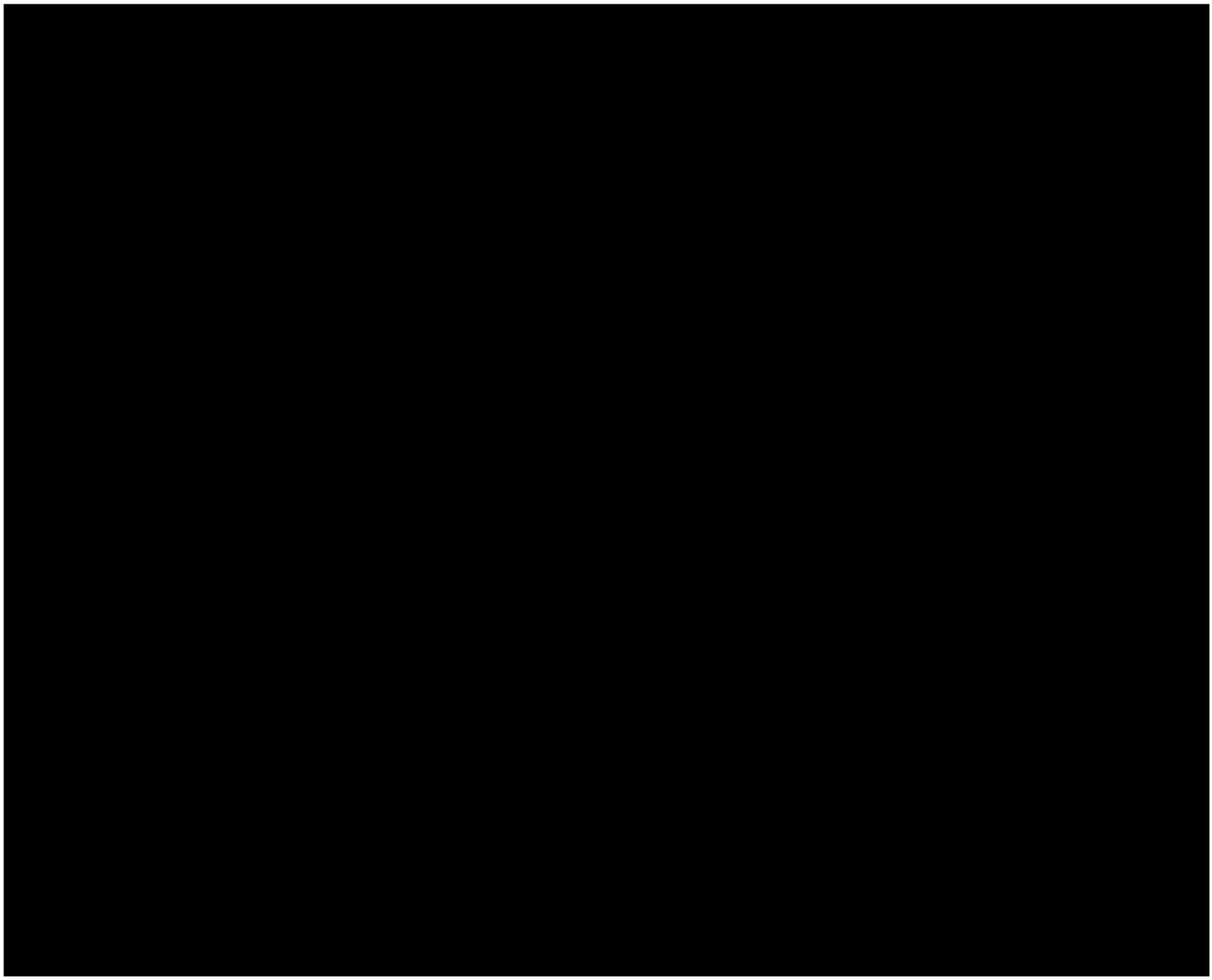
Procedures will be repeated as detailed from section 7.4.3 (steps 1-8).

[redacted]

3. Slit lamp biomicroscopy assessment will be conducted according to the guidelines set out in the CVI Grading scales
4. Exit visual acuity with habitual spectacles or spectacle refraction (using same method and refraction as entry).
5. The subject will be discharged and will sign the exit statement.

7.4.6 Summary of Visits and Procedures

Table 2 summarizes the visits and procedures for the study.



8 Adverse Event Reporting

8.1 Adverse Event Definitions

An ‘adverse event’ refers to any undesirable clinical occurrence in a subject, whether it is considered to be device-related or not. Adverse events (AE) may be classified as ‘unanticipated adverse device effects,’ ‘serious adverse events,’ ‘significant adverse events,’ or ‘non-significant adverse events,’ as defined below.

Classification	Definition
Serious Adverse Event	Those events that are life-threatening, or result in permanent impairment of a body function, or permanent damage to a body structure or necessitate medical (therapeutic) or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
Significant Adverse Event	Those non-serious adverse events that occur with contact lens usage that are not sight-threatening but are usually symptomatic and may warrant therapeutic management and /or temporary or permanent discontinuation of contact lens wear.
Non-Significant Adverse Events	Those less severe non-serious adverse events that occur with contact lens usage that are not sight-threatening, may or may not be symptomatic and may warrant palliative management, such as ocular lubricants or temporary interruption of contact lens wear.
Unanticipated Adverse Device Effect	Adverse events in a clinical trial that were not previously identified in the protocol in terms of nature, severity, or degree of incidence. An Unanticipated Serious Adverse Device Effect is an unanticipated adverse event that is serious in nature and caused by or associated with the device and is considered reportable.

AE classification, coding (for reporting to the sponsor) and examples are provided in the following table of Contact Lens Adverse Event Classification and Reporting table:

Code	Condition	Reporting
Serious Adverse Events		
01	Presumed infectious keratitis or infectious corneal ulcer	Notify sponsor as soon as possible, **within 24 hours;** IRB reporting as per requirements
02	Permanent loss of ≥ 2 lines of best spectacle corrected visual acuity (BSCVA)	
03	Corneal injury that results in permanent opacification within central cornea (6mm)	
04	Uveitis or Iritis (e.g. presence of anterior segment inflammation as described in ISO 11980, Annex B)	
05	Endophthalmitis	
06	Hyphema	
07	Hypopyon	
08	Neovascularization within the central 6mm of cornea	
00	Other serious event	
Significant Adverse Events		
11	Peripheral (outside central 6mm), non-progressive, non-infectious ulcer	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
12	Symptomatic corneal infiltrative event	
13	Superior epithelial arcuate lesions (SEALs) involving epithelial split	
14	Corneal staining ≥ dense coalescent staining up to 2mm in diameter (e.g. moderate, ISO 11980 grade 3)	
15	Corneal neovascularization ≥ 1.0mm vessel penetration (e.g. ≥ ISO 111980 Grade 2), if 2 grade change from baseline	
16	Any temporary loss of ≥ 2 lines BSCVA for ≥ 2wks	
17	Any sign and/or symptom for which subject is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	
10	Other significant event	

Non-significant Adverse Events		
21	Conjunctivitis (bacterial, viral or allergic)	Notify sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11890 Grade 2), if 2 grade change from baseline	
23	Asymptomatic corneal infiltrative events	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	

NOTE: The Clariti lens is associated with a high level of conjunctival staining (grade 3 or more). Therefore, this characteristic staining will not be classified as an adverse event in this study **unless in the investigator's opinion it is severe or is associated with other adverse ocular health changes**.

[redacted]

8.2 Procedures for Adverse Events

Treatment of an adverse event will depend on its nature and severity. Based on the clinical judgment of the investigator the subject may be referred to an ophthalmologist for treatment. The investigator will attempt to determine whether the reaction is related to the test device or a result of other factors. An Adverse Event Form will be completed for each adverse event. If both eyes are involved, a separate Adverse Event Form will be completed *for each eye*. Whenever possible, the adverse event will be photo-documented.

Expenses incurred for medical treatment as part of study participation will be paid by the sponsor (bills and prescription receipts kept). The subject must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

8.3 Reporting Adverse Events

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to subject participation will be reported to the Principal Investigator and the sponsor within 24 hours of the investigator becoming aware of the event. The Principal Investigator will report the event to the IRB as soon as possible (by fax, mail/delivery, phone, or email). All fatal or life threatening events will be reported immediately to the IRB.

Significant and Non-Significant Adverse Events will be reported to the sponsor as soon as possible, but no later than 5 working days after the occurrence.

sponsor contact details are:

8.4 Discontinuation from the Study

A subject's study participation may be discontinued at any time if, in the opinion of the sponsor or the investigator it is in the best interest of the subject. All discontinuations will be fully documented on the appropriate study forms and the Discontinuation Form will be completed.

9 Device Malfunctions

A device malfunction means the failure of the device to meet its performance specification or otherwise perform as intended. *Any defective lens that is likely to cause or contribute to a Serious Adverse Event should be reported to the Principal Investigator and the sponsor* ***within 24 hours*** *of the investigator becoming aware of the malfunction.*

Other defective lenses should be reported to the sponsor as soon as possible.

This clinical study will also ascertain satisfaction or preference with subjective attributes such as comfort, vision, or lens handling. Responses to these subjective questionnaires will not be considered as complaints or Device Malfunctions.

10 Statistical Analysis

10.1 Sample size

Approximately 80 subjects will be enrolled with a goal that approximately 60 will be completed. Based on historical clinical data a sample size of 60 completing subjects is sufficient to detect a mean difference of 0.5 (0 – 10) in subjective ratings assuming α=0.05 and a power of 80% (Table 3).

Table 3: Sample Size Calculations

Mean individual difference in score	Mean individual standard deviation	Sample size, Power 80% (p = 0.05)	Sample size, Power 85% (p = 0.05)
0.5	1.3	56	63

10.2 Statistical analysis

De-identified data will be provided to the sponsor by each site for the sponsor to perform the analyses. Each site will only have access to the data collected at their site.

Summary statistics will be produced (e.g. mean, standard deviation). Non-inferiority testing will be performed as appropriate. Paired t test will be used to compare slit lamp biomicroscopy, lens fit and subjective scores between study lens types. Repeated Measures Analysis of Variance (ANOVA) or paired analysis will be used to compare the variables between study visits. The critical level for statistical significance will be set at $p \leq 0.05$.

All participants who were evaluated will be used in the analysis. In the event of missing data, individual data points will be excluded in the analysis and not extrapolated from the collected data. A detailed statistical analysis plan will be outlined in the report.

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11 Data Quality Assurance

[redacted]

11.2 Record keeping

Detailed records of all study visits will be made using the Case Report Forms (CRFs). All data recorded on forms will be in ink. Any corrections to the forms will be initialed and dated at the time they are modified.

11.3 Record retention

Following study completion, data will be available in electronic and/or paper format for audit, sponsor use, or subsequent analysis. The original clinical raw data (including completed CRFs and Informed Consent forms) will be retained according to guidelines set forth in the general work agreement with the site. The sponsor will be notified and consulted if ever the files are to be destroyed. In the event that this implementation document is indicated for design verification and validation purposes, as indicated on the title page, all original raw data forms and completed CRF's will be forwarded to the sponsor at completion of the final report.

11.4 Data Entry / Data Management

Data will be entered into an electronic spreadsheet. Study staff will only be able to modify the data file via password entry. The investigators will be responsible for the data integrity, and complete data entry for each visit as well as the take home questionnaires. The investigator will send the data collected to the study sponsor within approximately 10 business days after the last subject completes the final visit. In addition, a full one-month dataset will be provided to the sponsor at the sponsor's request. Investigators will be masked for the interim analysis.

11.5 Confidentiality

This study is confidential in nature. Details of confidentiality are covered within the Master Agreement signed between the sites and the sponsor.

All records will also be handled in accordance with HIPAA (1996) standards.

11.6 Publication

Publication conditions are laid out in the Master Agreement signed between the sites and the sponsor.

12 Study Costs

The sponsor will compensate the clinical site and the subjects for their time and participation in this voluntary study.

[redacted]