Study document: Protocol

A DISPENSING CLINICAL TRIAL OF INVIGOR I DAILY DISPOSABLE LENS AGAINST CLARITI 1-DAY LENS

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Study Sponsor Representative: [redacted] Date: [redacted]

CooperVision Sponsor Management [redacted] Date: [redacted]

Site Principal Investigator: [redacted] Date: [redacted]

Site Principal Investigator: [redacted] Date: [redacted]

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[redacted]

1 Introduction

CooperVision is evaluating the clinical performance of its silicone-hydrogel lens referred to as the Invigor I Daily Disposable contact lens compared to the commercially available clariti 1-day contact lens when worn over one week for each lens type in a randomized, bilateral, cross-over, dispensing study on a daily disposable basis.

[redacted]

2 Study Objective

This is a study to evaluate the clinical performance of the Invigor I Daily Disposable (DD) lens compared against the commercially available clariti 1-day lens when worn on a daily wear modality over one week for each lens type.

The primary variables of interest are:

- Lens fit performance

The secondary variable of interest is:

- Subjective comfort ratings

[redacted]

3 Study Design

This will be a prospective, double-masked, randomized, bilateral, 1 week cross-over, dispensing study comparing the Invigor I DD lens against the clariti 1-day lens. Each participant will be randomized to wear either the Invigor I DD or the clariti 1-day as a matched pair first. Both study lenses will be used in a daily disposable lens wear modality for one (1) week. It is anticipated that this study will involve 3 scheduled visits:

- Visit 1: Enrollment/ Screening/ Baseline/Fitting/Dispensing of lens pair #1
- Visit 2: 1-week follow-up visit for lens pair #1 (6-10 days after dispensing pair #1), and dispensing visit of lens pair #2
- Visit 3: 1-week follow-up visit for lens pair #2 (6-10 days after lens pair #2 dispense) and exit.

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 Part 812 Investigtional Device Exemptions
- Ethical principles of the Declaration of Helsinki
- Principles of US and ICH Good Clinical Practice

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 Southern California College of Optometry. The conduct of this study will be approved by [redacted] 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

The Sponsor will register this study 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 Participants

This study will recruit at two clinical sites, the Clinical Optics Research Lab (CORL) at Indiana University and Southern California College of Optometry (SCCO). Up to 80 subjects will be recruited across both sites with the aim of completing 50 subjects across both sites. Each subject will be given an 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 (average wearing of 8 hours/day and 5 days/week) without the need of using rewetting drops
- Requires spectacle lens spherical powers between -1.00 to -5.75 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:

- Is presently participating in any other clinical or research study including eye related clinical or research study.
- Has never worn contact lenses before.
- Has any systemic disease affecting ocular health.
- Has any active ocular pathology or severe insufficiency of lacrimal secretion (moderate to severe dry eyes) that would affect the wearing of contact lenses.
- Is using any systemic or topical medications that will affect a study outcome variable, and/or ocular health.
- Has any known sensitivity to fluorescein dye or products to be used in the study.
- 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 pregnant, lactating, or planning a pregnancy at the time of enrolment (by verbal confirmation at the screening visit).

7.2 Study Materials

7.2.1 Contact lens

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

[redacted]

Details of the contact lenses are shown in Table 1.

Table 1: Study lenses

	Invigor I DD	clariti 1-day
Material	[redacted]	somofilcon A
Base Curve (mm)	8.6	8.6
Lens Diameter (mm)	14.1	14.1
Power (D)	-1.00 to -6.00 (0.25 steps)	-1.00 to -6.00 (0.25 steps)

7.2.2 Contact lens care

No contact lens care system is required for this study as lenses are daily disposable lenses to be worn for a single day only with new lenses worn each day.

7.2.3 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.

Participants will not be allowed to use rewetting drops during the course of the study.

7.2.4 Storage of Lenses and Lens Care Solutions

The study materials must be stored in a secured area. All lenses and lens care solutions should be stored at controlled room temperature (59-86°F).

7.2.5 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.

In the event that lenses need to be replaced due to damage/defects before the next scheduled visit, only the damaged/defective lenses will be replaced. A log of lens replacement will be recorded by the site.

7.2.6 Disposal of Consumables

This study provides consumables (lenses) to participants for use during the study. Participants will be instructed to dispose of worn lenses (both Invigor I DD and control lenses) daily. Lenses worn

for the scheduled visits will be collected from the participants and they may be either returned to the Sponsor or disposed, as detailed in the implementation protocol.

Lenses with product observations (e.g. moderate lens deposits), product defects, or product quality complaints will be collected and returned to CooperVision at the completion of the study. All unworn lenses will be collected from each study participant.

7.2.7 Masking and Control of Study Materials

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

7.2.8 Ordering and Accountability of Study Materials

The study 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.

7.3 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 participant that they are able to attend the follow-up visits within the visit window and wearing schedule before enrolling them in the study.

It is anticipated that this study will involve 3 scheduled visits:

- Visit 1: Enrollment/ Screening/ Baseline/ Fitting/ Dispensing of lens pair #1 (either Invigor I DD or control lens);
- Visit 2: 1-week follow-up assessment of lens pair #1, & dispense of lens pair #2 (either Invigor I DD or clariti 1-day lens), 6-10 days after dispense of lens pair #1;
- Visit 3: 1-week follow-up assessment of lens pair #2, 6-10 days after lens pair #2 dispense and exit.

Visits that fall outside of the specified visit windows may be considered as unscheduled visits.

The Invigor I DD lenses will be worn for one week (6-10 days) and the clariti 1-day lenses will be worn for one week (6-10 days).

At the completion of the one week period of wear with the first pair of lenses, there will be a break of 10 minutes, followed by a dispense and assessment of the second pair of lenses. At the completion of the last visit, participants will exit the study.

7.3.1 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 distance (4m) visual acuity with habitual spectacles or spectacle refraction
6. Auto refraction/auto keratometry: Flat and Steep K readings (D)
7. Sphero-cylindrical refraction (D), monocular distance visual acuity (HIHC) (logMAR)
    - The endpoint of this 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).
8. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI Grading scales (Appendix 1).
9. 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.
10. The subject will be assigned a randomization ID and the first pair of contact lenses will be selected according to the randomization table.
11. Initial contact lens power chosen based on vertexed, spherical equivalent obtained from refraction. The initial contact lens power will be kept the same for both study lenses (i.e. based on empirical powers).

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]

   a. [redacted]
   b. [redacted]
   c. [redacted]

[redacted]

4. [redacted].
5. [redacted]

   a. [redacted]
   b. [redacted]
   c. [redacted]

6. Monocular logMAR visual acuity (4M) will be recorded with high contrast letters under high and low room illumination*.

   a. [redacted]
   b. [redacted]

[redacted]

7. The subject will be asked to give subjective ratings post lens settling

   a. Comfort (0-10 scale) and comments
   b. [redacted]
   c. [redacted]
   d. [redacted]

8. [redacted]

[redacted]

[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.
    a. Corneal coverage at all times (y/n)
    b. Lens centration (optimal /slightly decentered, <0.5mm /extremely decentered >0.5mm, NTSI)
    c. [redacted]
    d. Post-blink movement (mm)
    e. Primary gaze lag (mm)
    f. Upgaze lens lag (mm)
    g. Lens push-up tightness (%)
    h. Overall lens fit acceptance (0-4 scale, and yes/no) and investigator reason, if unacceptable.
    i. Overall lens fit impression (-2 to 2 scale)
10. The subject will be encouraged to wear the study lenses as much as they normally do with their habitual lenses and for a minimal of 5 days/week.
11. The subject will be instructed to discard study lenses at home nightly but to keep lenses with problem to return to the site.
12. The subject will be given enough contact lenses to wear until the next study visit.
13. The subject will be discharged and reminded to return for the one week visit of the first pair.

7.3.2 Visit 2: Follow-up Pair #1/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]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- Comfort at insertion, during the day, end of the day and overall comfort since the last visit (0-10 scale)
- [redacted]

2. [redacted]

[redacted]

4. [redacted]

type

5. Monocular lens fit will then be assessed and graded according to CVI grading scales (Appendix 2).
    a. Corneal coverage at all times (y/n)
    b. Lens centration (optimal /slightly decentered, <0.5mm /extremely decentered >0.5mm, NTSI)

    [redacted]

    d. Post-blink movement (mm)
    e. Primary gaze lag (mm)
    f. Upgaze lens lag (mm)
    g. Lens push-up tightness (%)
    h. Overall lens fit acceptance (0-4 scale, and yes/no) and investigator reason, if unacceptable.
    i. Overall lens fit impression (-2 to 2 scale).

[redacted]

7. Slit lamp biomicroscopy will be assessed according to the guidelines set out in the CVI grading scales.

Lens Dispensing Pair # 2

1. There will be a break before insertion of pair 2 (of at least 10 minutes).
2. The second lens pair will be applied (according to the randomization table). The lenses will be inserted by the subject from the blister pack.
3. The use of saline for rinsing prior to insertion is permitted if necessary.

Procedures will be repeated as detailed in Visit 1 for pair 2 from section 7.3.1 (steps 2-13 in Dispensing pair#1 section).

7.3.3 Visit 3: One Week Visit Pair 2/Study Exit

This visit will occur 6-10 days after dispense of lens 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 for assessment of pair # 2 will be followed (similar to assessment of pair #

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.

7.3.4 Summary of visits and procedures

Table 2 summarizes the visits and procedures for the study.

Table 2: Summary of Visits and Procedures

8 Adverse Event Reporting

8.1 Adverse Event Definitions

An 'adverse event' refers to any undesirable clinical occurrence in a participant, 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
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	reporting as per requirements
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	

Normal or adaptive symptoms

Transient symptoms such as end-of-day dryness, lens awareness, itching or burning or other discomfort may occur with contact lens wear and may occasionally reduce wearing time. ***These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.***

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 Adverse Events.

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.

10 Statistical Analysis

10.1 Sample size

Approximately 70 subjects will be enrolled with a goal that approximately 50 will be completed. Based on historical clinical data a sample size of 50 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)
0.5	1.2	48

10.2 Statistical analysis

Summary statistics will be produced (e.g. mean, standard deviation). 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 alpha level for statistical significance will be set at $p \leq 0.05$, with adjustment for multiple comparisons.

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.

11 Data Quality Assurance

[redacted]

[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 5 business days after the last subject completes the final visit.

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]

13 Appendices