Centre for Contact Lens Research

School of Optometry
& Vision Science,
University of Waterloo,
Waterloo, Ontario, Canada.
N2L 3G1
Tel: 519-888-4742
Fax: 519-888-4303

http://cclr.uwaterloo.ca

Protocol

COMPARISON OF DAILY DISPOSABLE INVIGOR I (TEST) AND SELECT 1 DAY LENSES) (SAGE PHASE-BC1)

CCLR Study number: P/564/16/CV
Sponsor Study Code: CV-16-43
Version Number: 2.0
Document Date: 20 Sep, 2017
Sponsor Company: CooperVision, Inc.

	Reviewed and approved (Name and Signature)	Date DD/MM/YY
Principal investigator		
Lead investigator		
Protocol author		
Quality assurance		
Sponsor		

Study Personnel

Principal investigator:	[redacted]
Clinical Research Manager:	[redacted]
Protocol author:	[redacted]
Lead investigator:	[redacted]
Statistical adviser:	[redacted]
Sponsor contact:	[redacted]
Sponsor Management	

DOCUMENT CHANGE HISTORY

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

TABLE OF CONTENTS

Confidentiality

This is a private document and the property of the Centre for Contact Lens Research. It is therefore confidential to the recipient and must not be quoted from or distributed beyond the company to which it is sent without the express written permission of the Director (or her/his designate) of the Centre for Contact Lens Research. Release of information from this document is governed by the research agreement on file.

Disclaimer

This study will be conducted for research purposes only and is not intended to be used to support safety and efficacy in a regulatory submission.

1 INTRODUCTION

Small changes in lens design, the process of fabricating contact lenses, and changes to packaging solutions can have an impact on their on-eye performance and comfort. CooperVision is evaluating the clinical performance of an investigational silicone-hydrogel lens called Invigor I (test) when worn on a daily disposable wear modality over 1 week (for each lens) in a randomized, bilateral, cross-over, dispensing study. [redacted] The study lenses are specifically designed to be a daily disposable wear silicone hydrogel contact lens, replaceable after each use.

2 STUDY OBJECTIVE

The purpose of this study is to investigate the overall clinical performance of the Invigor IA (test) daily disposable silicone hydrogel lens compared to the Invigor IB (control) lens that is identical to the marketed lens Select 1 Day, and is labelled with an investigational label for the purpose of this study.

This is a study to validate the performance of Invigor 1 (test) lenses when worn on a daily disposable wear modality over 1 week (for each lens).

The primary variables of interest are:

- Comfort and preference (subjective ratings)
- Vision (logMAR, and subjective ratings)
- Anterior ocular health (corneal staining and conjunctival staining, etc.)
- Discontinuation rate

[redacted]

2.1 STUDY HYPOTHESIS

The study hypothesis is that the Invigor IA lens (test) will perform as well as or better than the Invigor IB (control lens) in terms of the primary outcome variables evaluated.

Further, that there will be no contraindications to continued lens wear with the Invigor IA (test) lens when worn on a daily disposable basis.

3 STUDY DESIGN

This will be a, prospective, double-masked, randomized, bilateral, 1 week cross-over, dispensing study comparing the Invigor IA (test) lens against the Invigor IB (i.e. Select 1 Day) (control) lens. Each participant will be randomized to wear either the test or control as a matched pair first. Both test and control 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 (either test or control lens);
- Visit 2: 1-week follow-up visit for lens pair #1, and dispensing visit of lens pair #2 (either test or control lens) 6-10 days after lens pair #1 dispense;
- Visit 3: 1-week follow-up visit for lens pair #2 (6-10 days after lens pair #2 dispense) and exit.

The study design is shown in Figure 1.

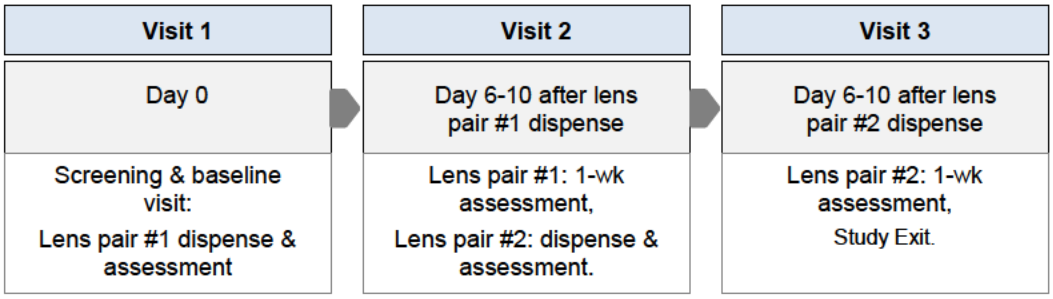

Figure 1: Study design

Each participant will be randomized to wear either the test or control as a matched pair first. Both test and control lenses will be used in a daily disposable lens wear modality.

4 ETHICS REVIEW / STATEMENT OF COMPLIANCE

4.1 RELEVANT STANDARDS / GUIDELINES

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

- ISO 14155 Clinical Investigation of Medical Devices for Human Subjects
- ICH Harmonized Tripartite Guideline for Good Clinical Practice
- The University of Waterloo's Guidelines for Research with Human Participants
- Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition
- 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.

This protocol will be submitted to and reviewed through the Office of Research Ethics (ORE) at the University of Waterloo.

The conduct of this study has been approved at the Institutional Review Board at University of Waterloo, Canada, through ORE file number 21616.

4.3 INFORMED CONSENT

Informed consent shall be obtained in writing from the participant prior to their enrollment in the study, and before any procedure specific to the clinical investigation is carried out.

5 CLINICAL TRIAL REGISTRATION

This study will be registered in the clinical trials registry (www.ClinicalTrials.gov) by the study sponsor.

6 POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

This is a minimal risk study. The investigational contact lenses used in this study are intended for daily wear (not extended wear) with usage consistent with typical daily wear.

This study is considered to be a non-significant risk study based on United State Food and Drug administration (FDA) and International Standards Organization (ISO) guidelines due to the daily wear nature of the study.

Further, the investigational lens will be tested for sterility and biocompatability prior to release.

Complications that may occur during the wearing of contact lenses include discomfort, dryness, aching or itching eyes, excessive tearing, discharge, hyperemia and variable or blurred vision and infiltrates. More serious risks may include photophobia, iritis, corneal edema or eye infection.

Although contact lens-related infections are very infrequent, the possibility does exist. The incidence of infection due to day-wear soft lenses is 0.035%. Almost always an infection will occur only in one eye. This risk is assumed by 35-million Americans who currently wear contact lenses. The lenses being used may not have the exact prescription power needed by the participant (within +/-0.25 of their required contact lens powers). It is possible that some participants may experience minimal "eye strain" when focusing through this reduced/extra power which may cause headache.

Routine clinical procedures including auto-refraction, auto-keratometry, visual acuity, anterior ocular health assessment, and contact lens fitting will be used. In addition, high magnification imaging (including video and still images) of the lens fit may be made using 35 mm or digital cameras.

There might not be direct benefits to the participants in this study. However, participation in a study may contribute to scientific research information that may be used in the development of new contact lens products. In addition, participants will receive an examination of the front part of their eyes and may have the opportunity to try a different type of soft contact lenses at no cost to them.

7 MATERIALS AND METHODS

7.1 RANDOMIZATION

A randomization schedule will be generated. The final study randomization schedule will be generated by the Head of the CCLR Data Management Team, and provided to the research assistants for the study. Study investigators will remain masked to the randomization schedule until the study is completed and the database is locked.

7.2 Masking

Both participant and investigator will be masked as to lens type and lens assignment (control vs. test). The contact lens coding will be masked to both the investigators and participants as much as possible. A computer generated randomization scheme (sample randomization in Appendix 14) will be used and will be provided to an unmasked member of staff at the study site. Study investigators will remain masked to the randomization schedule until the study is completed and the database is locked. Lenses dispensed to participants may be over-labelled, however the safety information on the outer package label of the contact lens, shall be clearly visible.

Under normal circumstances, the investigator mask will not be broken until all subjects have completed the study and the database is finalized, the subject mask will not be broken until their involvement in the study is complete. 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 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 Participants

Up to 40 participants will be successfully enrolled and dispensed/randomized with the study products, with a target of 30 participants completing the study. Participants will be recruited using CCLR records and advertising approved by the UW Office of Research Ethics (Appendices 2 &11). Informed consent will be obtained for all participants prior to their enrolment in the study (Appendix 1).

Each participant will be given a unique ID number. Additionally, all participants must meet the study inclusion and none of the exclusion criteria listed below.

7.3.1 INCLUSION CRITERIA

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

- Is at least 17 years of age and has full legal capacity to volunteer;
- Has had a self-reported oculo-visual examination in the last two years;
- Has read, understood, and signed the information consent letter;
- Is willing and able to follow instructions and maintain the appointment schedule;
- Has a visual acuity of 20/30 or better (in each eye) with their habitual vision correction, or 20/20 best-corrected vision (for binocular distance acuity);
- Must be able to achieve 20/30 or better (in each eye) with the study lenses;
- Currently wears soft contact lenses for at least 3 days per week, 8 hours each day;
- Requires spectacle lens powers between -0.75 and -06.50 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.

7.3.2 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).

* For the purposes of this study, active ocular disease is defined as infection or inflammation which requires therapeutic treatment. Mild (i.e. not considered clinically relevant) lid abnormalities (blepharitis, meibomian gland dysfunction, papillae), corneal and conjunctival staining and dry eye are not considered active ocular disease. Neovascularization and corneal scars are the result of previous hypoxia, infection or inflammation and are therefore not active.

7.3.3 REPEATED SCREENINGS

In some circumstances a repeated screening may need to be scheduled. Examples include, but are not limited to:

a) Incomplete information available at time of screening to determine eligibility (e.g. current lens brands worn, history from current eye care practitioner etc.)
b) Study procedures unable to be completed in time scheduled for visit;
c) Study products not available at the time of the screening visit;
d) A transient health condition which may affect the eye(s) (e.g. a common cold, active allergies, fatigue etc.)
e) The short term use of medications (e.g. antibiotics, antihistamines etc.)

f) Reassessment of baseline ocular conditions (e.g. corneal and/or conjunctival staining, scars etc.)

The maximum total number of screenings permitted will be 3.

7.4 STUDY MATERIALS

7.4.1 CONTACT LENS

Participants will be randomized to receive either the test or control lens as a matched pair at each visit per a predetermined randomization schedule (Appendix 14). The lenses (test and control) will be labelled as Invigor IA (test) and Invigor IB (control).

The Invigor IA (test) lens is an investigational product and will be subject to pre-clinical assessment before being released for the study. This lens is not commercially available in Canada and therefore an ITA (investigational testing authority) from Health Canada has been received.

The Invigor IB (control) i.e. Select 1 Day lens is approved by FDA and Health Canada, and is commercially available in Canada and the USA, however for the purpose of this study, it has been labelled as Invigor IB and is covered under an ITA issued by Health Canada.

Details of the Invigor IA (test) and Invigor IB (control) study lenses used in this study are shown in Table 1. The test lens is the Invigor IA (test) lens and approved by Health Canada for use in the study.

Table 1: Study lenses used in this study

	Invigor IA (test)	Invigor IB (control) (i.e. Select 1 Day)
Manufacturer	CooperVision	CooperVision
HC License No.	-	81009
Material	somofilcon A	somofilcon A
Health Canada license #	-	81009
EWC (%)	56%	56%
Dk/t (-3.00D)	86.0	86.0
BOZR (mm)	8.6	8.6
Diameter (mm)	14.0	14.0
Sphere power (D)	-1.00 to -6.00 (0.25 steps)	-1.00 to -6.00 (0.25 steps)

7.4.2 CONTACT LENS CARE SYSTEM

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.

7.4.3 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 encouraged to use rewetting drops; however, those who habitually used rewetting drops will be allowed to continue using their normal drops. Rewetting drop use will be recorded at each visit.

7.4.4 STORAGE OF LENSES AND LENS CARE SOLUTIONS

The study materials must be stored in a secured area. All lenses and any lens care solutions used to store worn lenses should be stored at controlled room temperature (59-86°F). The lens care solution used will be specified in the implementation protocol.

7.4.5 CLINICAL SUPPLY INVENTORY

The CCLR must keep an accurate accounting of the study product during the study. A detailed inventory (including lenses received, dispensed, unused, and returned to the Sponsor) must be completed for study supplies. The study supplies are to be used in accordance with the instructions given to participants 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 (CCLR).

7.4.6 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 test and control lenses) daily, but retain the foils of all used lens packs and return them at their next study visit. 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. Any extra lenses not used in the study will be returned to CooperVision.

7.4.7 MASKING AND CONTROL OF STUDY MATERIALS

The contact lenses coding will be masked to both the investigator and participant. If standard labelling does not sufficiently mask the study material then over labelling will be performed. However

the safety information on the outer package label of the contact lens will not be covered and shall be clearly visible.

7.4.8 ORDERING AND ACCOUNTABILITY OF STUDY MATERIALS

Both the Invigor IA (test) and the Invigor IB 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.

7.5 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 contact lenses will be provided to participants by a research assistant / study coordinator / technician or the investigator (lenses will be provided to the investigator without unmasking the investigator).

The investigator should confirm with the participant that they are able to attend the follow-up visits within the visit window 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 test or control lens);
- Visit 2: 1-week follow-up assessment of lens pair #1, & dispense of lens pair #2 (either test or control 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 IA (test) lenses will be worn for one week (6-10 days) and the Invigor IB (control) lenses will be worn for one week (6-10 days). Lens assessment visits will occur with each pair of lenses with options as described in Table 2.

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.

Table 2 lists a summary of the study visits.

Table 2: Summary of study visits

Visit #	Visits	Visit length
1 – 0*	Screening and fitting	0.5 hrs
1 – 1*#	Lens pair #1: dispense and baseline assessment	1.0 hrs.
2#	Progress assessment of lens pair #1, and dispense of lens pair #2 (6 to 10 days after lens pair #1 dispense)	1.5 hrs.
3	Progress assessment of lens pair #2, and Exit from Study (6 to 10 days after lens pair #2 dispense)	1.0 hrs.

* The 1-0 and 1-1 visits may be combined (to total 1.5 hrs)

Lens pair #1 and Lens pair #2 may be either the Invigor IA (test) or Invigor IB (control)

7.5.1 VISIT 1: SCREENING / BASELINE VISIT / DISPENSING PAIR #1

Participant will be assigned a unique participant/Study ID number after signing the ICL. The investigator will determine participant eligibility using the inclusion and exclusion criteria. Ineligible participants will be discontinued from the study.

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

- The patient is expected to attend the screening / baseline visit not wearing their habitual contact lens products.
- The participant will be required to read and sign an Informed Consent Form prior to enrolment. When the participant has signed the consent form, the participant will be considered to be enrolled in to the study.
- Participant demographics and medical history (age, sex, race and ethnicity, medical conditions, medications, allergies)
- Contact lens history (own lens information, and wear time)
- Baseline visual acuity with spectacles or spectacle refraction.
- Auto refraction/auto keratometry: Horizontal and Vertical K readings (D)
- Sphero-cylindrical refraction (D), and best sphere refraction (D) & monocular & binocular distance visual acuity (high contrast) (logMAR)
- Slit lamp biomicroscopy will be assessed according to the approved study biomicroscopy CRF (Appendix 4).

- The investigator will confirm that the patient meets the criteria set out in the inclusion criteria, and none of the exclusion criteria and is eligible to continue in the study.
- The participant 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.
- Contact lens power and fit may be evaluated at the screening visit or at the baseline visit.

[redacted]

- The contact lenses will be dispensed by a research assistant / study coordinator / technician (in a manner which does not unmask the participant and investigator).
- The lenses will be inserted by the participant from the blister pack as described in Section 7.4.3 of the Protocol.
- The contact lenses will be fitted and allowed to settle (Appendix 3).
- Initial subjective ratings (Appendix 16) include:
    - Initial comfort (0-100 scale) and comments

      [redacted]
    - Vision quality / clarity (0-100 scale) and comments

      [redacted]
- 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 participant will be allowed to sit for 10 minutes to allow for the lenses to settle.
- Monocular over refraction will be done to determine if a different power is needed.

  [redacted]
- Change lens prescription to that noted by over-refraction, if needed. Repeat subjective ratings after lens settling.

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

[redacted]

- Lens fitting assessment, according to the guidelines in Appendix 3.
- Monocular lens surface and fit will then be assessed and graded according to the CVI grading scales (Appendix 5).

[redacted]

- The participant will be instructed to wear the study lenses for at least 8 hours, and 5 days per week.
- Participants will be provided contact lenses for wear till the next scheduled visit.

- At end of visit the participant will be reminded to return for the next scheduled visit of the first pair.

7.5.2 VISIT 2: ASSESSMENT OF PAIR #1 AND DISPENSING PAIR #2

This visit will occur 6-10 days after dispense of lens pair #1.

Participants will be asked to wear lenses for **at least two hours** prior to the visit appointment. Participants who attend without wearing lenses for the specified period will be rescheduled.

- The participant will be asked to score their subjective response as detailed in CVI Grading scales (Appendix 18D).
- The following will be recorded at the one week visit.
    - Hours of lens wear prior to the appointment

      [redacted]
    - Binocular comfort at insertion, during the day, end of the day, during the last week
    - Overall comfort (0-100 scale), during the last week

      [redacted]
    - Binocular vision quality / clarity of vision during the last week (0-100 scale)
    - Binocular vision quality / clarity of vision at night during the last week if applicable (0-100 scale)

      [redacted]
    - Comments by participants
- Unscheduled lens replacements (Y/N) OD and / or OS
- Monocular and binocular logMAR visual acuity (4M) will be recorded with high contrast letters under high and low room illumination.
- Monocular lens surface and fit will then be assessed and graded according to the CVI grading scales. [redacted]

- The lenses will be removed and retained in the CCLR (see Section 7.4.6 for disposing consumables).
- Slit lamp biomicroscopy will be assessed according to the approved study biomicroscopy CRF (Appendix 4).
- There will be a break before insertion of pair 2 (of 10 minutes).
- The same procedures will be followed for pair 2 as mentioned in section 7.5.1.
- The contact lenses will be dispensed by a research assistant / study coordinator / technician (in a manner which does not unmask the participant and investigator).
- The lenses will be inserted by the participant from the blister pack as described in Section 7.4.3.

Procedures of lens assessment and dispense will be repeated as detailed in section 7.5.1 for Baseline visit / Dispensing Pair #1.

7.5.3 VISIT 3: ASSESSMENT OF PAIR # 2 AND STUDY EXIT

This visit will occur 6-10 days after dispense of lens pair #2.

Procedures for assessment of pair # 2 will be followed (similar to assessment of pair # 1) as detailed in the follow up visit section 7.5.2.

- Participant will also rate their overall preference between lens pair #1, lens pair-#2 or no preference (and reason for preference) for a number of considerations that include:
    - Overall comfort preference, and reason for preference.
    - Overall vision preference, and reason for preference.

[redacted]

- The lenses will be removed by the participant and retained in the CCLR (see section 7.4.6 for disposing consumables).
- Slit lamp biomicroscopy assessment will be conducted according to the CVI approved study biomicroscopy CRF, using sodium fluorescein dye.
- Exit visual acuity will be performed with habitual glasses.
- The participant will be discharged and will sign the study completion forms.

7.5.4 SUMMARY OF VISITS AND PROCEDURES

Table 3 summarizes the visits and procedures for the study.

Table 3: Summary of Visits and Procedures

	Visit 1 *Screening / Baseline & Dispensing lens pair #1*	**Visit 2** *Follow-up of lens pair #1/ Dispensing lens pair #2*	**Visit 3** *Follow-up of lens pair #2 and Exit*
Informed Consent	√		
Meet inclusion/exclusion criteria	√		
History at baseline	√		
Demographics	√		
VA with spectacles or refraction	√		√

	Visit 1 *Screening / Baseline & Dispensing lens pair #1*	Visit 2 *Follow-up of lens pair #1/ Dispensing lens pair #2*	Visit 3 *Follow-up of lens pair #2 and Exit*
Auto-refraction & keratometry	√		
Sphero-cylindrical refraction	√		
Best corrected (sphero-cyl) VA monocular and binocular	√		
Best corrected sphere	√		
Biomicroscopy	√	√	√
[redacted]		[redacted]	[redacted]
Symptoms & problems	√	√	√
[redacted]	[redacted]		
Dispense new lenses	√	√	
Participant ratings (at scheduled visit)	√	√	√
Surface assessments	√	√	√
[redacted]	[redacted]	[redacted]	[redacted]
Over Refraction	√	√	
VA with contact lenses	√	√	√
Assessment of adverse events	√	√	√
Exit study			√

8 MONITORING PROTOCOL ADHERENCE

Adherence to study visit windows, lens wearing schedule, and time windows around other data collection points (i.e. subjective ratings) will be monitored internally by the CCLR and reported as deviations from the windows described in the protocol in the weekly reports and study report.

9 ADVERSE EVENT REPORTING

9.1 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.

A number of conditions may result in temporary discontinuation until resolution. These include corneal infiltrates, corneal staining, limbal injection, bulbar injection or bulbar and tarsal conjunctival abnormalities.

See SOP012_v01_Adverse Event Management and Reporting for a description of adverse events, including management and reporting.

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 participant 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	

9.1.1 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.

9.2 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 participant 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 (Appendix 6) 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 participant must be followed until resolution or no further change is anticipated and/or referred for further care with the appropriate health care professional and/or recorded as being under appropriate health care as per investigator's discretion. A written report will be completed indicating the subsequent treatment and resolution of the condition.

9.3 REPORTING ADVERSE EVENTS

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to participant's participation will be reported to the Principal Investigator and the sponsor within 24 hours of the investigator becoming aware of the event. The Investigator will report the event to the IRB as per IRB requirements (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.

Reporting/notification of **<u>all adverse events</u>** will be made to **Clinical Operations, CooperVision**

[redacted]

9.4 DISCONTINUATION FROM THE STUDY

A participant'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 participant. All discontinuations will be fully documented on the appropriate study forms and the Discontinuation Form will be completed. Participants discontinued from a study will be reimbursed $20 per hour for their active involvement in the study (including the initial screening visit).

- The list of possible reasons for discontinuation from the study: Screening failure: Participants will be discontinued if they do not meet the inclusion and exclusion criteria outlined in section 7.3.
- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort and /or vision and/ or fit with the study products.
- Positive slit lamp finding: Participants may be temporarily or permanently discontinued from the study depending on the severity of the condition and on the judgement of the investigator.
- Adverse event: If a participant experiences an adverse event during the study they may be discontinued based on the clinical judgement of the investigator.
- Symptoms: If the participant has persistent symptoms they may be discontinued based on the clinical judgement of the investigator.
- Disinterest, relocation or illness: The participant may choose to discontinue due to reasons within or beyond their control.
- Violation of protocol or non-compliance: The participant will be discontinued if they are unable or unwilling to follow the protocol specified visit schedules and/or study procedures.
- Instillation of topical ocular medication: The participant will be discontinued if they elect to use a topical ocular medication during the study unless that topical ocular medication is prescribed for a limited duration (less than two weeks) to treat a transient condition; in this case the participant may remain an active participant (at the discretion of the investigator) after stopping topical ocular medication following resolution of the ocular condition).
- Lost to follow-up: The participant will be discontinued if they cannot be contacted and do not return for a final exit visit, and if the investigator has made a reasonable effort to contact the participant for a final study visit.

- Premature termination of the study by the sponsor, the CCLR or the Office of Research Ethics at the University of Waterloo.

A discontinuation form (Appendix 8) will be completed, which requires the signatures of both the participant and the investigator except where the participant is lost to follow-up in which case only the signature of the investigator is required.

10 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 (usually in weekly study updates to the Sponsor).

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.

11 STATISTICAL ANALYSIS

11.1 SAMPLE SIZE

Approximately 40 participants will be dispensed in order to target a total of approximately 30 participants completing the study. [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

11.3 STATISTICAL ANALYSIS

All data will be analyzed by the CCLR at the University of Waterloo. Summary statistics will be produced (e.g. mean, standard deviation). Data analysis will be conducted using Statistica, SPSS or SAS. Descriptive statistics will be provided on information regarding baseline variables (age, gender, refractive error distribution, etc.), and follow up visits (e.g. mean, SD). Analysis of variables will be conducted separately on each eye, and data will not be pooled. For assessments conducted for each eye separately, the right eye will be used for analysis if there is no difference between eyes. If a general difference is found (e.g. for paired t-test / Wilcoxon matched pairs) between OD and OS, a comment will be provided.

A Binomial test will be used to analyze the results for the count data of subjective preferences. The number of "no preference" will be evenly distributed to the two options on the basis they would be equally likely to choose either.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The critical alpha level for statistical significance will be set at $p \leq 0.05$, with no adjustments for multiple comparisons.

All participants who were evaluated will be used in the analysis. In the event of missing data, individual data points may be excluded in the analysis and not extrapolated from the collected data.

12 DATA QUALITY ASSURANCE

12.1 STUDY MONITORING

Site qualification of the investigative site has been completed to ensure that the site facility is adequate, personnel are qualified and resources are satisfactory to conduct clinical studies for the Sponsor. The protocol will be reviewed by the investigators prior to enrollment of the first participant. This will involve an overview of the protocol, which includes information on study objectives, inclusion and exclusion criteria, study visits and adverse event reporting. Data collection forms will also be reviewed and this will provide an opportunity to discuss any questions.

Central study monitoring will involve regular study updates from the clinical site to the sponsor. The updates will include the number of participants enrolled, the number eligible, the number completed and whether there have been any unscheduled visits, discontinuations, significant or serious adverse events or major protocol deviations. These updates will be provided weekly.

Prior to final data lock, a close-out visit/discussion may be warranted to check for accuracy and completeness of records. 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.

12.2 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.

12.3 RETENTION OF STUDY RECORDS AND DATA

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 CCLR SOP014_v01. The Sponsor will be notified and consulted if ever the files are to be destroyed. Copies of all original raw data forms and completed CRF's will be forwarded to the sponsor at completion of the final report.

Records and data from this study will be retained for a minimum of 25 years.

12.4 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 in the CRFs and other relevant forms. At the completion of the study the investigator will send the data collected to the study sponsor within approximately 5 business days after the study report is finalized.

Data analysis will not be conducted on comments which have been recorded in the source documents. Only relevant and applicable comments will be included in the final report as deemed necessary by the lead investigator.

13 PROTOCOL TRAINING

All delegated study personnel will be required to complete training prior to their involvement in the study.

14 STUDY MONITORING

Status reports will be provided to the study sponsor by email on a regular basis.

[redacted]

Sponsor monitoring visits may be conducted throughout the study and will be scheduled by the study sponsor in conjunction with the lead investigator. In addition study records may be inspected at the CCLR by the sponsor, the sponsor's designate, the Office of Research Ethics at the University of Waterloo, and by regulatory authorities in Canada and the United States, namely Health Canada and the United States Food and Drug Administration (FDA); however, no records containing identifiable/personal information will be permitted to leave the custody of the CCLR.

15 PROTOCOL DEVIATIONS

Protocol deviations are unanticipated or unintentional changes to a study after it has received prior sponsor approval and ethics clearance. Protocol deviations can be major or minor.

Major protocol deviations may impact the research protocol, Informed Consent form or other study materials, usually cannot be anticipated ahead of time and are often necessary to ensure the safety and welfare of the participants.

The following are examples of protocol deviations that must be reported to the IRB:

1. Changes in procedures initiated to eliminate immediate risks/hazards to participants;
2. Enrolment of participants outside the protocol inclusion/exclusion criteria;
3. Inadvertent deviation in specific research intervention procedures or timing of the research intervention which could impact upon the safety or efficacy of the study-related intervention or upon the experimental design;
4. Informed Consent documentation violations: no documentation of informed consent; incorrect version of, or incomplete, informed consent documentation used.

Minor protocol deviations are caused by or which originate with research participants and normally are not reported to the IRB unless these result in increased risk to the participants. The following are examples of protocol deviations that are considered minor and do not require reporting to the IRB:

- Logistical or administrative aspects of the study (e.g., study participant missed appointment, change in appointment date or time);
- Inadvertent deviation in specific research intervention procedures or timing of the research intervention which would not impact upon the safety or efficacy of the study-related intervention or upon the experimental design (i.e., missing a measurement during a session that is not considered critical for the study).

15.1 REPORTING AND DOCUMENTING PROTOCOL DEVIATIONS

Major protocol deviations which require changes to the research protocol or informed consent process/document or other corrective actions to protect the safety, welfare, or rights of patients or others must be reported to the IRB according to the site's guidelines. All protocol deviations (major and minor) occurring during the study will be documented and included in the final report and data safety monitoring report to the IRB.

16 CONFIDENTIALITY

This study is confidential in nature. All information gathered during this study is proprietary and should be made available only to those directly involved in the study. Information and reports arising from this project are the property of the sponsor.

17 PUBLICATION

Due to the confidential and proprietary nature of the clinical study, any presentation and/or publication including but not limited to those made at scientific meetings, in-house, in peer-review journals, professional publications, etc. need to be approved by the sponsor.

18 STUDY COSTS

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

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

18.1 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit a study completion form (Appendix 9) will be completed, which requires the signatures of both the participant and the investigator.

Once their involvement in the study is complete, participants receive a Letter of Appreciation (Appendix 10).

Participant remuneration will be up to $90 for completing the study. Full details are given in the relevant information and consent letter (Appendix 1).

19 STUDY REPORT

A report will be sent to the sponsor according to terms described in the study contract.

20 APPENDICES

SAGE Appendix 1A ICL-dispensecrossover_31may2017

SAGE Appendix 2 Advertisements 13jul2016

SAGE Appendix 3 Screening and fitting form 02aug2016

SAGE Appendix 4 Biomicroscopy form 03nov2016

SAGE Appendix 5 Progress evaluation form 02aug2016

SAGE Appendix 6 -CCLR Adverse Events form 13jan2016

SAGE Appendix 7 Form106 ORE AE form

SAGE Appendix 8 Discontinuation form 12jun2016

SAGE Appendix 9 Study completion form 12jun2016

SAGE Appendix 10 Letter of Appreciation 02aug2016

SAGE Appendix 11A Email script (HTML) 31may2017

SAGE Appendix 12 Study remuneration 12jun2016

SAGE Appendix 14 Sample Randomization Tables 21jul2016

SAGE Appendix 15 Emergency Wallet Card 12jun2016

SAGE Appendix 16E Subjective ratings on lens insertion crossover phases 12jun2016

SAGE Appendix 18D Subjective ratings at follow-up visits crossover phases 02aug2016

SAGE Appendix 24 CVI Adverse Event Notification Form 27mar2015

SAGE Appendix 25 CVI Adverse Event Outcome Form 27mar2015

SAGE Appendix 26 Medical history form 07nov2014

SAGE Appendix 27 Protocol Deviation Form 12jun2016

SAGE Appendix 28 Product Observation Form 02aug2016

SAGE Appendix 29 Study Exit Form 02aug2016