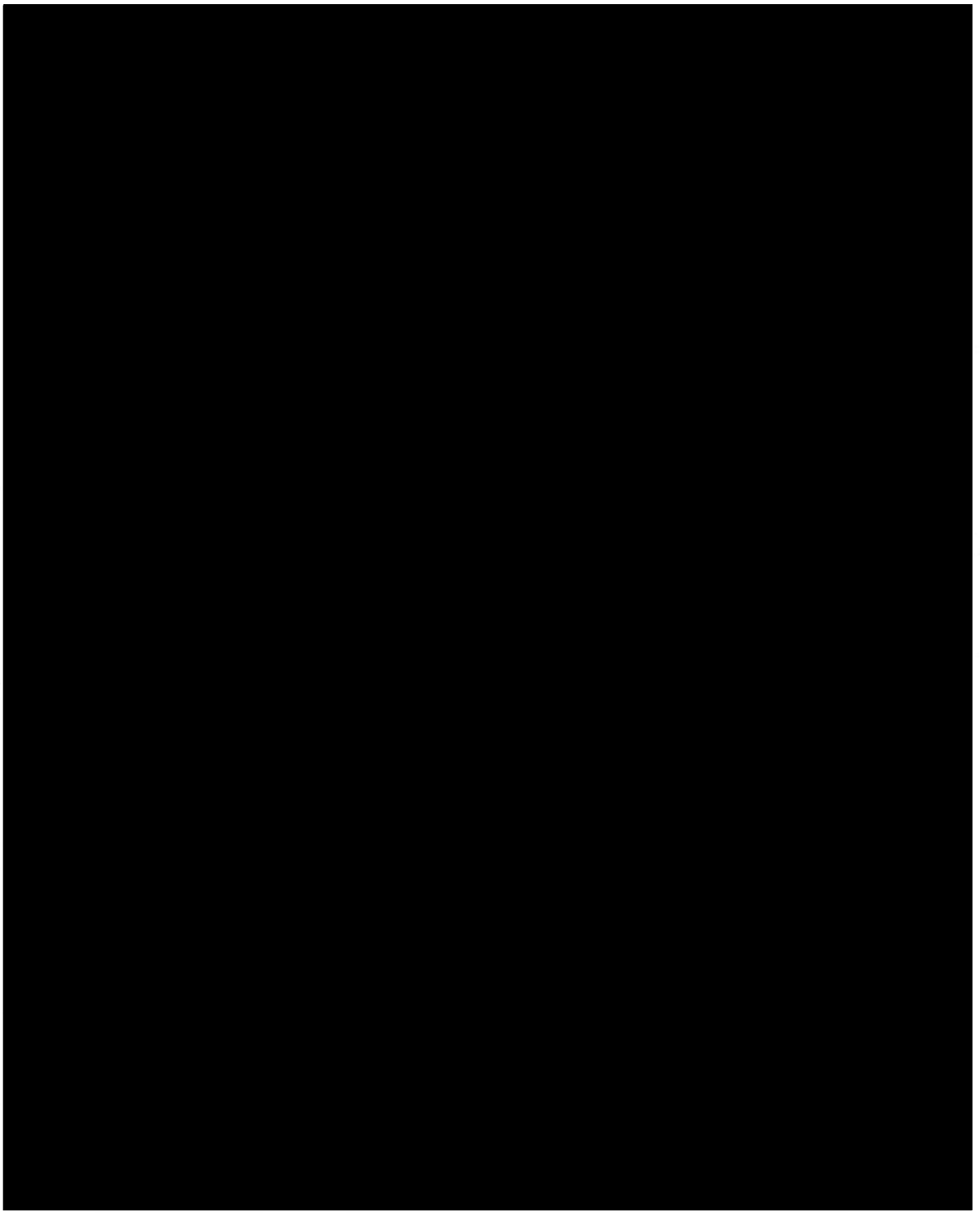

CORE
Centre for Ocular Research & Education

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Optometry & Vision Science

Centre for Ocular Research & Education (CORE),
School of Optometry & Vision Science | University of Waterloo, 200 University Avenue West | Waterloo, ON, Canada N2L 3G1
+1 (519) 888-4742 | CORE.uwaterloo.ca

Protocol

Comparing habitual daily disposable silicone hydrogel (DDSH) contact lens wearers to habitual daily disposable hydrogel (DDH) contact lens wearers and non-lens wearers (BAGPIPES)

Sponsor Company	CooperVision, Inc.
Sponsor Study number:	EX-MKTG-89
CORE Study number:	[redacted]
Version Number:	2.0
Document Date:	28nov2020
Document Type:	Study protocol
Clinical Sites:	CORE, University of Waterloo
	Eurolens Research, Manchester, UK

[redacted]

DOCUMENT CHANGE HISTORY

Version #	Originator/s	Description of change(s)	Date
1.0	Amir Moezzi	Original protocol	27 Feb 2018
1.1	Amir Moezzi	Reviewer edits in general Removed reference to a Pilot Study Changed primary objective & primary variable Revised contact lens wear history inclusion criteria Contact lens details specified	04 Apr 2018
1.2		Page 10, Re matching ethnicity in study Groups: Added ”this is due to possible differences in physiological response to corneal hypoxia in Asian and non-Asian participants”. Page 14, inclusion criterion #6: Changed “BVS” to “vertexed spherical equivalent” Page 15, inclusion #10: Clarified that this criterion is not-applicable to participants in group 3. Page 15: Added “topical anesthetic” to exclusion # 6. Page 16: Added “due to potential ocular physiological changes, such as changes in the corneal shape and cell types” in the end of exclusion #9. Page 17, 4.7.2 Contact lens care system: Added The study lens will inserted directly from sterile saline in the standard lens vial (sealed by the manufacturer). Page 17, 4.7.3 Rewetting drops & saline, Added: Worn lenses will be collected from the participants’ lens-wearing eye at the end of the 3-hour wearing period (or on discontinuation/exit from the study) and will be disposed as described section 4.7.6 of the protocol. Page 18, Table 2: V1 has been changed to V0 for day 1.	28 May 2018

Version #	Originator/s	Description of change(s)	Date
		Page 24, Potential risks: Equalized denominators of rates of AEs by revising to “in approximately twenty people in a population of 10,000 who wear soft contact lenses on an extended wear basis”. Page 25, Potential risks: Added “In rare situations, some individuals may experience vaso-vagal syncope (or similar symptoms) with the use of topical anesthetic or ocular examination procedures” Page 25, Potential risks: Reference to “An examination of the front part of their eyes” has been removed as a benefit to the participant.	
1.3	Amir Moezzi	Page 10-11, study group inclusion criteria description: changed to DD CL wear for the past (minimum) 6 months and CL wear in the same material category in the past (minimum) 3 years. Removed maximum of 7 years CL wear experience. Added no previous history of PMMA CL wear. Page 14-15, study inclusion criteria: revised to reflect the above-mentioned changes in the inclusion criteria.	29Nov2018
1.4	Amir Moezzi	Changed the study design to multi-site and reflected this minor change throughout the protocol.	12Jul2019
1.5	Amir Moezzi	Section 4.8.1. Added CE marking in Table 1. Section 4.9.3. Changed ‘required to remain within CORE’s premises’, to “required to remain in the study site”. Section 7. Changed “UW SOP012” to “Adverse Event Standard Operating Procedures (SOP) document for the relevant study site”. Typo (Appendix 16) has been removed from the end of the sentence. Section 10. Clarified that Eurolens Research will follow their local standard procedures and forms for study completion and any required feedback to participants.	04Oct2019

Version #	Originator/s	Description of change(s)	Date
		Section 12.5. Added retention period of 20 years for Eurolens Research. Section 15.1.3. Provided clarification that Eurolens Research study site will follow their local ethics committee requirements for reporting protocol deviations to the respective ethics committee.	
1.6	Amir Moezzi	Section 4.8.3. Typo corrected from 4.7.6. to 4.8.6. Section 4.8.5. Clarification provided for ordering consumables. Corrected name of “Eurolens Research” site throughout the protocol. Section 8. Clarified reimbursement rate as “$20 per hour in CORE and it will be based on the rate approved by the respective ethics committee for Eurolens Research study site. Section 10. Added participant remuneration provided by Eurolens Research will be based on the amount approved by the respective ethics committee. Section 12.1. Re study updates, changed to “regular study updates from *each site* to the sponsor” instead of “regular study updates from *CORE* to the sponsor”	08Oct2019
1.7	Amir Moezzi	4.1.1 Clarified that trial fitting of study lenses is done in day 1. Section 4.6: Clarified that Eurolens Research may use a different terminology for the ICL (for example, ICF or PIS). Section 4.7.2: Replaced “CORE” with “study site in exclusion criterion#2” Section 8: added flat fees for participant discontinuation at Eurolens. Section 4.9.2: Changed the order of subjective and objective redness measurements.	10Oct2019

Version #	Originator/s	Description of change(s)	Date
		Section 4.9.2: Clarified that trial fitting of the study lens (randomized eye) will be conducted in groups 1 and 2 (CI wearers) only.	
1.8	Amir Moezzi	Section 4.1.1. Study visits: Clarified washout period of at least 1 day (24 hours) before to the 2nd study day and that the second study day should occur within maximum of 30 days from the first study day Section 4.9.3. Study Day 2: Clarified washout period of at least 1 day before the 2nd study day and that the second study day should occur within maximum of 30 days from the first study day. Section 4.10. Moved CL fitting to after confocal microscopy in the summary of procedures for clarification.	02Mar2020
1.9	Amir Moezzi	Sections 4.1.1, 4.9.1 Table 2, 4.9.2 and 4.10 (throughout the protocol) Removed trial fitting of the study lenses from V0. This is a COVID-19 consideration to reduce the time in close proximity with participants. Sections 4.1.1, 4.7.2, 4.8.4 and 4.9.3 (throughout the protocol) Clarified that inclusion criterion #12 for acceptable lens fit and comfort will be evaluated after fitting study lenses in V1 (Study Day2). Section 4.7.1. Changed maximum number of participants to 26 in each group. Section 4.8.1. Removed Health Canada license# for study lenses from Table1. Also, clarified that study lens is no longer licensed by Health Canada or marketed in Canada and that an investigational testing authorization from Health Canada will be obtained prior to recruitment.	27Aug2020
2.0	Amir Moezzi	Section 4.7.1. Clarified that Groups 1 and 2 will be recruited at both CORE (Canada) and Eurolens (UK). These participants will be exposed to the study contact lens on the second day of the study. There will be competitive recruitment between the two sites. Section 4.7.1. Clarified that Group 3, the non-lens wearing group, will all be recruited at CORE (Canada). These participants will	28Nov2020

Version #	Originator/s	Description of change(s)	Date
		only attend the first study visit and will not be exposed to the study contact lens.	

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Confidentiality

This is a private document and the property of the Centre for Ocular Research & Education. 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 Ocular Research & Education. 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 & BACKGROUND

Current contact lenses are available in either silicone hydrogel (SH) or hydrogel (H) materials. Silicone hydrogel lenses are far more transmissible to oxygen (they have higher Dk/t) and this is believed to be beneficial for maintaining healthy corneal metabolism. Several publications highlight this by showing less redness around the cornea (less limbal redness with SH compared to H) and the eye in general (less bulbar redness with SH compared to H). [1-3] The severity of corneal infections has also been reported to be reduced with SH lenses compared to H lenses. [4, 5]

Napping and sleeping in contact lenses has been reported as a common occurrence,[6, 7] It is known that, even with no contact lens wear, the limbus may become redder and the cornea swells when the eye is closed [8, 9] due to the uptake of water as a result of anaerobic corneal metabolism with eye closure, and deswells upon eye opening. It is of interest to understand whether habitual wear of hydrogel contact lenses modifies this redness and/or the swelling or deswelling response due to the lower level of oxygen through the lens during habitual lens wear.

This non-dispensing, randomised study is designed to evaluate differences in ocular physiological responses to a 3-hour period of monocular closed eye lens wear of a low Dk/t hydrogel (HEMA) lens, between habitual Daily Disposable Silicone Hydrogel (DDSH) lens wearers and habitual Daily Disposable Hydrogel (DDH) lens wearers.

Daily disposable wearers will be used because this replacement modality is being fit more often than re-useable lenses in many countries around the world. A 3-hour period has been chosen in this study because this length of time is anticipated to be sufficient to induce limbal redness and will induce a sufficient corneal swelling response to measure a change in corneal thickness from baseline,[10, 11] meaning that we do not require the participants to wear the lenses overnight. The reduction in redness and deswelling of the cornea will be followed for 3-hours. This should be sufficient time for the average corneal thickness to return to levels that are very close to baseline values. [12] Limbal redness and corneal thickness will fully recover to baseline values and there will be no permanent changes as a result of this study. [12-15]

2 OBJECTIVES

The primary objectives of this study are:

To compare baseline data between 3 groups - *habitual wearers of DDSH / habitual wearers of DDH / non-lens wearers* - in terms of:

- Limbal & bulbar redness

- Corneal vessel ingrowth

And to compare data post closed eye lens wear in 2 groups - *habitual wearers of DDSH / habitual wearers of DDH* - in terms of:

- Limbal & bulbar redness

The primary study measures are:

- Limbal & bulbar redness (Oculus Keratograph 5)
- Corneal vessel ingrowth (slit-lamp photography & image analysis)

3 HYPOTHESIS

The study main hypotheses are:

1) There will be greater corneal vessel ingrowth in habitual wearers of DDH than DDSH and non-lens wearers at baseline.
2) There will be greater limbal & bulbar hyperemia response following 3 hours of wearing a low Dk HEMA CL in habitual wearers of DDH than DDSH and non-lens wearers.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This study is a multi-site, prospective, randomized, non-masked, unilateral, non-dispensing study. The first part of the study (Day 1) involves collecting measures from three groups of participants (see group descriptions below). The second part (Day 2) only involves the two contact lens wearing groups (Group 1 & Group 2) and involves comparing between habitual wearers of DDSH and DDH for corneal swelling response & recovery following wearing a low Dk HEMA CL in a randomized eye under eye closure conditions for 3 hours. The contralateral control eyes with no lens wear will remain open during the test period.

Study Group inclusion criteria description:

The following 3 groups with age (within ± 5 years), ethnicity (being Asian vs. non-Asian, this is due to possible differences in physiological response to corneal hypoxia in Asian and non-Asian participants), and spherical contact lens power (within ± 2.00D) matched will be involved in this study:

GROUP 1: For the past (minimum) 6 months has ONLY worn spherical DDSH lenses AND prior to wearing this lens they only wore SH material lenses in the past (minimum) 3 total years.

GROUP 2: For the past (minimum) 6 months has ONLY worn spherical DDH lenses AND prior to wearing this lens they only wore H material lenses in the past (minimum) 3 total years.
GROUP 3: No previous experience of contact lens wear (no need to match Rx of this group).

Additional criteria:

For groups 1 & 2, currently and for at least the previous 6 months has had habitual daily disposable wear schedule of at least 8 hrs a day, 5 days a week in only one material category - either silicone hydrogel or hydrogel material.

For groups 1 & 2, no previous history of overnight wear or PMMA (polymethylmethacrylate) lens wear.

For groups 1 & 2, a minimum of 3 years of lens wear experience.

For group 3, no previous history of contact lens wear.

Study visits:

It is anticipated that this study will involve 2 days with at least 1 day in-between with no lens wear and no use of any rewetting drops (if applicable) as the washout period. The second study day should occur within maximum of 30 days from the first study day. The required minimum study washout period will be at least 1 day of no lens wear and no use of any rewetting drops (if applicable) on the day (24 hours) before the second study day. This study has up to a total of 7 scheduled visits:

Study Day 1

The first study day will be observational in nature for collecting comparison data across all 3 participant groups described above. There will be only one study visit on day 1.

Visit 0: This visit includes screening, confirmation of CL history, measurements of [redacted], slit-lamp biomicroscopy, [redacted] Then Day1 exit slit-lamp biomicroscopy [redacted]

Study Day 2

Only the study groups 1 & 2 will be involved in the second day of study. They will attend the study visit 1 on day 2 at 3 ± 0.5 hours after waking and eye opening in the morning, and wearing their habitual spectacles.

[redacted]

[redacted]

Visit 2:

[redacted]

Visit 4: 1hr after CL removal

[redacted]

Visit 6: 3hr after CL removal

[redacted] the objective ocular redness measurement OU [redacted]

Exit Visit:

[redacted]

Biomicroscopy including corneal staining, OU

Study exit [redacted]

Exit the study.

4.1.2 RANDOMIZATION

A randomization schedule will be generated using SAS or a web-based program: (www.randomization.com). The final study randomization schedule will be generated by CORE's Data Management Team, and provided to the research assistants and clinical investigators at each study site for use during the study.

4.1.3 MASKING

There will be no masking in this study. Masking of the Study investigators is not possible as they need to measure the study main variables in the predetermined randomized eye.

4.2 STATEMENT OF COMPLIANCE

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

- ISO 14155 Clinical Investigation of Medical Devices for Human Subjects, Parts 1 & 2
- 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. http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/
- Declaration of Helsinki

4.3 STUDY SITES

This study will be conducted at the following study sites:

- CORE, University of Waterloo, Canada
- Eurolens Research, University of Manchester, UK

4.4 ETHICS REVIEW

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, Canada and to the respective ORE at the University of Manchester, UK. Notification of ethics clearance of the application is required prior to the commencement of the study at each site. The conduct of this study will be given clearance by the Clinical Research Ethics Committee at the University of Waterloo, Canada, and the respective Research Ethics Committee at the University of Manchester, UK.

4.5 CLINICAL TRIAL REGISTRATION

This study will be registered in the clinical trials registry (https://clinicaltrials.gov/) by the study sponsor.

4.6 INFORMED CONSENT

Informed consent shall be obtained in writing from all participants prior to their enrolment in the study, and before any procedure specific to the clinical investigation is carried out. Based on local research ethics requirements, Eurolens Research may use a different terminology for the information consent letter/ICL (participant information sheet (PIS) and informed consent form/ ICF).

4.7 STUDY POPULATION

4.7.1 NUMBER OF PARTICIPANTS

Up to a maximum of 26 participants in each study group will be randomized, with a target of completing 17 in each of the three groups.

Groups 1 and 2 will be recruited at both CORE (Canada) and Eurolens (UK). These participants will be exposed to the study contact lens on the second day of the study. There will be competitive recruitment between the two sites and though unlikely, depending on recruitment progress, it is possible that all the subjects will be seen only at CORE (Canada) or only at Eurolens (UK). This means that a maximum of 52 and a minimum of 0 participants will be exposed to the study contact lens at each site.

Group 3, the non-lens wearing group, will all be recruited at CORE (Canada). These participants will only attend the first study visit/day and will not be exposed to the study contact lens.

Participants will be recruited using the study site records and advertising approved by the respective Office of Research Ethics (ORE). Each participant will be given a unique study specific ID number. Additionally, all participants must meet all the study inclusion and none of the exclusion criteria listed below.

4.7.2 INCLUSION AND EXCLUSION CRITERIA

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

1. Is between 17 and 60 years of age inclusive (age matching required between all 3 study groups), and has full legal capacity to volunteer;
2. Has had a self-reported oculo-visual examination in the last two years.
3. Has read and signed an information consent letter;
4. Is willing and able to follow instructions and maintain the appointment schedule;

5. No previous history of overnight contact lens wear or PMMA (polymethylmethacrylate) lens wear.
6. Auto-refraction vertexed spherical equivalent between +4.00 and -8.00 (prescription matching required between groups 1 & 2). This criterion is non-applicable to participants in group 3.
7. Is found to be in one of the study groups matched by age (±5 years), ethnicity (Asian vs. non-Asian) and CL Rx (±2.00 D) according using the following criteria:

GROUP 1: For the past (minimum) 6 months has ONLY worn spherical DDSH lenses AND prior to wearing this lens they only wore SH material lenses in the past (minimum) 3 total years.

GROUP 2: For the past (minimum) 6 months has ONLY worn spherical DDH lenses AND prior to wearing this lens they only wore H material lenses in the past (minimum) 3 total years.
GROUP 3: No previous experience of contact lens wear (no need to match Rx of this group).

8. For groups 1 & 2, currently and for at least the previous 6 months has had habitual daily disposable wear schedule of at least 8 hrs a day, 5 days a week in only one material category - either silicone hydrogel or hydrogel material. This criterion is not-applicable to participants in group 3.
9. Is willing to wear the study contact lens in the randomized eye for 3 hours of eye closure on the second study day. This criterion is not-applicable to participants in group 3.
10. Has clear and healthy corneas and anterior eye and no active* ocular disease;
11. Can achieve monocular HCVA of logMAR 0.10 or better in each eye with subjective refraction or pinhole.
12. Can achieve acceptable fit and comfort in the randomized eye with the study lens. This criterion will be confirmed at the baseline visit (V1). This criterion is not-applicable to participants in group 3.
13. Has a wearable pair of spectacles.

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

1. Is participating in any concurrent clinical trial;
2. Is unable/unwilling to provide permission for the study site to seek CL history from their eye care practitioner
3. Has any known active* ocular disease and/or infection;

4. Has a systemic condition that in the opinion of the investigator may affect a study measure or interfere with contact lens wear; this may include, but not be limited to, diabetes, hyperthyroidism, recurrent herpes simplex/zoster, Sjogren's syndromes, xerophthalmia, acne rosacea, Stevens-Johnson syndromes, and systemic connective tissue disorders e.g. rheumatoid arthritis.
5. Is using any systemic or topical medications that in the opinion of the investigator may affect a study measure;
6. Has known sensitivity to fluorescein dye, topical anesthetic, or products to be used in the study;
7. Appears to have any active* ocular pathology, ocular anomaly or severe insufficiency of lacrimal secretion (severe dry eye) that would affect the wearing of contact lenses;
8. Appears to have any signs of corneal inflammation or previous infection or corneal opacity/scar;
9. Is pregnant, lactating or planning a pregnancy at the time of enrolment (by verbal confirmation at the screening visit), due to potential ocular physiological changes, such as changes in the corneal shape and cell types;
10. Is aphakic;
11. Has undergone refractive error surgery, or has a history of any ocular surgery or injury.
12. Is a toric or multifocal contact lens wearer.

* 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.

Repeated screenings

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

1. Incomplete information available at time of screening to determine eligibility (e.g. current lens brands worn, history from current eye care practitioner etc.)
2. Study procedures unable to be completed in time scheduled for visit;
3. Study products not available at the time of the screening visit;

4. A transient health condition which may affect the eye(s) (e.g. a common cold, active allergies, fatigue etc.)
5. The short term use of medications (e.g. antibiotics, antihistamines etc.)
6. Reassessment of baseline ocular conditions (e.g. corneal and/or conjunctival staining, scars etc.)

The maximum total number of screenings permitted will be 3 i.e. 2 repeated screenings are allowed.

4.8 STUDY MATERIALS

4.8.1 LENSES

Details of study lenses are show in Table 1.

Table 1: Lens parameters to be used in this study

Manufacturer	CooperVision
Lens Name	PREFERENCE STANDARD
Material	tetrafilcon A
EWC (%)	43%
Centre thickness (mm) @ +6.00 D	0.26
Dk	9.3
Dk/t (+6.00D)	3.6
BOZR (mm)	8.3
Diameter (mm)	14.0
Sphere power (D)	+6.00 D
CE marking on the label	Yes

The study lens is no longer licensed by Health Canada or marketed in Canada. The investigational testing authorization for this study will be obtained from Health Canada by the study sponsor.

4.8.2 CONTACT LENS CARE SYSTEM

No contact lens care systems will be used in this study. The study lens will inserted directly from sterile saline in the standard lens vial (sealed by the manufacturer).

4.8.3 REWETTING DROPS & SALINE

No rewetting drops will be used in this study. In the event of lens binding a few drops of sterile saline solution may be instilled into the eye to loosen the lens and therefore facilitate safe lens

removal. A log of whether saline was used to aid lens removal will be maintained. Saline solution may also be used to rinse residual sodium fluorescein from the eyes after corneal staining assessment. Worn lenses will be collected from the participants' lens-wearing eye at the end of the 3-hour wearing period (or on discontinuation/exit from the study) and will be disposed as described section 4.8.6 of the protocol.

4.8.4 CONTACT LENS FIT AND WEAR

This is not a dispensing study. The fit of study contact lens will be evaluated on the randomly determined study eye during the baseline visit (Visit 1, Study Day 2) to ensure acceptable lens parameters and fit. After placing the study lens on the randomized eye, slit lamp examination will be conducted to confirm acceptable lens fit and comfort, and the absence of debris underneath the lens. Only participants with acceptable lens fit and comfort in the randomized eye will be eligible to continue in the study. The study lens will then remain on that eye for 3-hours and the eye will be lightly covered to keep it completely closed. Complete eye closure will be attained through the use of gauze and surgical tape, covered by a loosely-fitting ophthalmic eye patch which does not create excess pressure on the eye. The contralateral (no-lens) eye will remain open during the 3 hour period.

4.8.5 ORDERING CONSUMABLES

A stock of study lenses will be provided by the Sponsor to CORE. CORE will distribute the lenses to any other study site.

Each study site must maintain an accurate accounting of the study product during the study. A detailed inventory must be completed for study contact lenses for the study product accountability. Unused lenses will be disposed of after discussion with CORE.

The disposable covers for confocal microscopy will be purchased by each study site. CORE will reimburse Eurolens Research for consumables, and CORE will be reimbursed by the study sponsor.

4.8.6 DISPOSING OF CONSUMABLES

This study will not provide any consumables (lenses and/or lens care solution) to participants for use during the study. Worn lenses will be collected from the participants' lens-wearing eye at the end of the 3 hour wearing period (or on discontinuation/exit from the study) and at the end of the study they will be disposed of according to UW/study site guidelines, unless otherwise directed by the study Sponsor. Worn lenses specifically associated with adverse events/product observations may be retained either at the study site or returned to CooperVision. Typical analysis in these cases relates to inspection for damage and/ or bacterial contamination.

4.8.7 PRODUCT ACCOUNTABILITY

Accountability logs will be kept to include the number of lenses received, dispensed, unused, and returned to vendor (where relevant). All lenses dispensed to participants will be recorded in the lens accountability log.

4.9 SCHEDULED AND UNSCHEDULED VISITS

4.9.2 STUDY DAY 1 (VISIT 0)

The first study day will be observational in nature for collecting comparison data across all 3 participant groups described above. There will be only one study visit (visit 0) in day 1.

Visit 0 (2.75 hours): This visit includes screening, confirmation of CL history, measurements of [redacted] slit-lamp biomicroscopy, [redacted]

At the screening, all participants who sign the informed consent letter will be assigned a study ID number. The investigator will determine participant eligibility using the inclusion and exclusion criteria. Ineligible participants will be discontinued from the study. The procedures to be performed in visit 0 are outlined below:

- The participant is expected to attend the screening visit 6-8 hours after waking. The participants in groups 1 and 2 (CL wearers) will attend, having inserted their CLs 0.5 hours after waking that day. Participants in group 3 will attend this visit with habitual spectacles, if any.
- The participant will be required to read and sign an Informed Consent Form [redacted] prior to enrollment. When the participant has signed the consent form, the participant will be considered to be enrolled in the study.
- Participant demographics and medical history (age, sex, medical conditions, medications, allergies).
- Contact lens history (habitual lens information and wearing habits) (N/A in group 3).
- Participants will be asked to review and sign a permission request to seek CL history from their eye care practitioner.
- Contact lens removal (N/A in group 3).
- [redacted]
- [redacted]n Slit lamp biomicroscopy.
- [redacted]
- Slit lamp biomicroscopy [redacted]
- Confirmation of study eligibility and continuation
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Day1 exit Slit lamp biomicroscopy assessments including corneal & conjunctival staining (safety measure).
- [redacted]

4.9.3 STUDY DAY 2 (VISITS 1 TO 6) & STUDY EXIT

Only the study groups 1 & 2 will be involved in the second day of study. There will be a washout period of at least 1 day between study days 1 and 2 with no lens wear and no use of any rewetting drops (if applicable) on the day before the second study day as a minimum washout. The second study day should occur within maximum 30 days from the first study day. Participants will attend the study visit 1 on day 2 at 3 ± 0.5 hours after waking and eye opening in the morning, and wearing their habitual spectacles. They are required to remain in the study site in-between visits during Day 2. The following study visits will occur in Day 2 (please refer to the Table 3 for the required study assessments for each visit in Day 2 :

[redacted]

Visit 2 (0.5 hours): Study assessments immediately after CL removal

Study assessments.

Visit 3 (0.5 hours): 0.5hr after CL removal study assessments

Visit 4 (0.75 hours): 1hr after CL removal study assessments

Visit 5 (0.5 hours): 2hr after CL removal study assessments

Visit 6 (1.25 hours): 3hr after CL removal study assessments and the study exit

Study Exit:

- After completing the study exit assessments, the study exit form will be completed when a participant exits the study. This form will be completed either at study completion, or if the participant is discontinued from the study at another time. A study exit form must be completed for all participants who have taken a study ID number. If in the opinion of the investigator post-study follow-up visits are required, the exit form will be completed after the last follow-up visit.
- The participant will be discharged and will sign the study completion forms and receive remuneration for participating in the study.

4.9.4 UNSCHEDULED VISITS

An unscheduled visit is defined as an interim visit requested by the participant or investigator due to an unanticipated problem. Data recorded at these visits will be entered into the database. Only relevant and applicable unscheduled visit information will be included in the final report as deemed necessary by the lead investigator.

4.10 SUMMARY OF STUDY PROCEDURES

Table 3 summarizes the visits and procedures for the study.

Table 3: Summary of visits and procedures for the study.

	Day 1 Attend V0 after 6-8 hrs of waking	Day 2 Attend V1 at 3 ± 0.5 hours after waking and eye opening in the morning, and wearing habitual spectacles.						
	V0 Screen & Observational data collection	V1 Baseline & CL insertion	V2 Immediately after CL removal	V3 0.5 hr after CL removal	V4 1hr after CL removal	V5 2hr after CL removal	V6 3hr after CL removal	V-Exit
Consent process	x							
CL history and wear schedule	x	x						
Health & medication	x	x						
Permission for CL History from eye care practitioner	x							
Habitual contact lens removal	x							
[redacted]	x							

	Day 1 Attend V0 after 6-8 hrs of waking	Day 2 Attend V1 at 3 ± 0.5 hours after waking and eye opening in the morning, and wearing habitual spectacles.						
	V0 Screen & Observational data collection	V1 Baseline & CL insertion	V2 Immediately after CL removal	V3 0.5 hr after CL removal	V4 1hr after CL removal	V5 2hr after CL removal	V6 3hr after CL removal	V-Exit
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	x							
Slit lamp biomicroscopy (with staining)	x							
[redacted]	[redacted]							
[redacted]	[redacted]							
[redacted]	[redacted]							
[redacted]	[redacted]							
[redacted]	[redacted]							
[redacted]	[redacted]							
[redacted]		x						
Exit Slit lamp (with staining)	x							x
[redacted]	[redacted]							[redacted]
[redacted]		x						

	Day 1 Attend V0 after 6-8 hrs of waking	Day 2 Attend V1 at 3 ± 0.5 hours after waking and eye opening in the morning, and wearing habitual spectacles.						
	V0 Screen & Observational data collection	V1 Baseline & CL insertion	V2 Immediately after CL removal	V3 0.5 hr after CL removal	V4 1hr after CL removal	V5 2hr after CL removal	V6 3hr after CL removal	V-Exit
[redacted]		[redacted]						
[redacted]		[redacted]						
[redacted]		[redacted]						
[redacted]		x	x	x	x	x	x	
Study completion and Exit								x

* Additional lenses may be dispensed at scheduled or U/S visits if there is lens defect, or lens damage.

** Not required if visit concurrent with previous one.

4.11 RECORDING FINDINGS OF INTEREST

The following variables may be recorded using a digital slit lamp system (video and still images):

- [redacted]
- Relevant corneal and conjunctival staining and/or other relevant findings in slit-lamp bomicroscopy
- [redacted]

5 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 study site. Deviations from the windows described in the protocol will be reported in the study report. Major protocol deviations will be reported to the Sponsor and the respective Office of Research Ethics (ORE) within 7 days of becoming aware of them (as per ORE's guidelines).

6 POTENTIAL RISKS AND BENEFITS TO HUMAN PARTICIPANTS

This is considered a minimal risk study because the study soft CL will be worn under closed eye conditions for only one single 3-hour period, for participants in groups 1 and 2 only. Group 3 will not wear a contact lens at all. The exact risks associated with this short period of closed eye contact lens wear is not reported in the literature, however the risks associated with daily wear (removal for eye closure) and with extended wear (repeated and successive overnight lens wear),) have been studied and are reported below.

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. More serious risks may include photophobia, iritis, corneal edema, or eye infection. In rare instances more serious complications may occur, including corneal ulcers (a sight threatening eye infection) which can result in corneal scarring, temporarily or permanently decreased vision and in some cases blindness. Although contact lens-related infections are very infrequent, the possibility does exist. The annual risk of Infections relating to contact lens wear occur in approximately four people in a population of 10,000 who wear soft lenses on a daily wear basis and in approximately twenty people in a population of 10,000 who wear soft contact lenses on an extended wear basis.

When contact lenses are worn on a daily wear basis there is a small risk of an adverse event compared to not wearing contact lenses. When contact lenses are worn on an extended wear basis (repeated overnights in succession), there is a significantly increased risk of an adverse reaction compared with wearing contact lenses on a daily wear basis. Over a period of one year, infiltrates occur in one to two people per population of 100 who wear soft contact lenses on a daily basis, and in four to eight people per population of 100 who wear soft contact lenses on an extended wear basis.

Additionally, it is possible that participants may experience mild and temporary discomfort associated with the study procedures /products/devices/eye drops (sodium fluorescein) including: burning and stinging, blurred vision, sandiness or grittiness, light sensitivity, dryness, itching, crusty eyes, foreign body sensation, and eye redness. The use of topical numbing (anesthesia) eye drops may also cause transient stinging and burning or, in rare occasions, an allergic reaction. In rare situations, some individuals may experience vaso-vagal syncope (or similar symptoms) with the use of topical anesthetic or ocular examination procedures.

There will be no direct benefits to the participants in this study. However, participation in this study may contribute to scientific research information that may be used in the development of new contact lens products. This study may help the study sponsor to better understand possible corneal structural/physiological differences among the study 3 groups.

7 ADVERSE EVENTS

7.1 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 Adverse Event Standard Operating Procedures (SOP) document for the relevant study site 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 study 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	For all serious AEs:
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)	Notify sponsor as soon as possible, **within 24 hours;** ORE reporting will be **within 24 hours** as per requirements
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**; ORE 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**; ORE 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	

7.2 NORMAL OR ADAPTIVE SYMPTOMS

Mild ocular symptoms such as dryness, itching or burning or other mild discomfort, and/or mild level signs of ocular redness, corneal/conjunctival staining, corneal endothelial blebs, stromal striae and folds, and central corneal epithelial clouding may occur with contact lens wear and eye closure. These are transient in nature and not reported as adverse events unless in the investigator's opinion they are unexpected in nature, and/or severity.

7.3 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 17) 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 deemed necessary as a result of study participation will be paid by the study site on behalf of the sponsor (bills and prescription receipts must be provided). 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.

7.4 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 Serious Adverse Events to the respective ORE within 24 hours of the investigator becoming aware of the event and as per ORE requirements (by fax, mail/delivery, phone, or email). All fatal or life threatening events will be reported immediately to the respective ORE.
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. The Investigator will report the event to the ORE as per ORE requirements (by fax, mail/delivery, phone, or email).

8 DISCONTINUATION FROM THE STUDY

Participants discontinued from the study will be reimbursed $20 per hour at CORE for their active involvement in the study (including the initial screening visit). Participants discontinued from a study at Eurolens Research study site will be reimbursed based on the rate approved by their respective ethics committee. 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. The following is a 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 4.7.2.
- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort 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, study site or the respective Office of Research Ethics.

A discontinuation form (Appendix 10) 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.

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. The respective ORE would also be notified within 24 hours of any device malfunction that may contribute to a Serious Adverse Event.*

Other defective lenses should be reported to the Sponsor as soon as possible (usually in weekly study updates to the Sponsor).

10 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit at CORE a study completion form will be completed, which requires the signatures of both the participant and the investigator. The participants will also be provided with a letter of appreciation.

Once their involvement in the study is complete at CORE, participants will be informed about receiving feedback following study completion in the Letter of Appreciation.

Participant remuneration will be $20 per scheduled protocol visit hour at CORE (including the initial screening visit and the periods between measurements on day 2), as specified in the information consent letter for CORE.

At Eurolens Research, participants will be remunerated based on the approved amount by the respective ethics committee as specified in the information consent letter for Eurolens Research.

Eurolens Research will follow their local standard procedures and forms for study completion and any required feedback to participants.

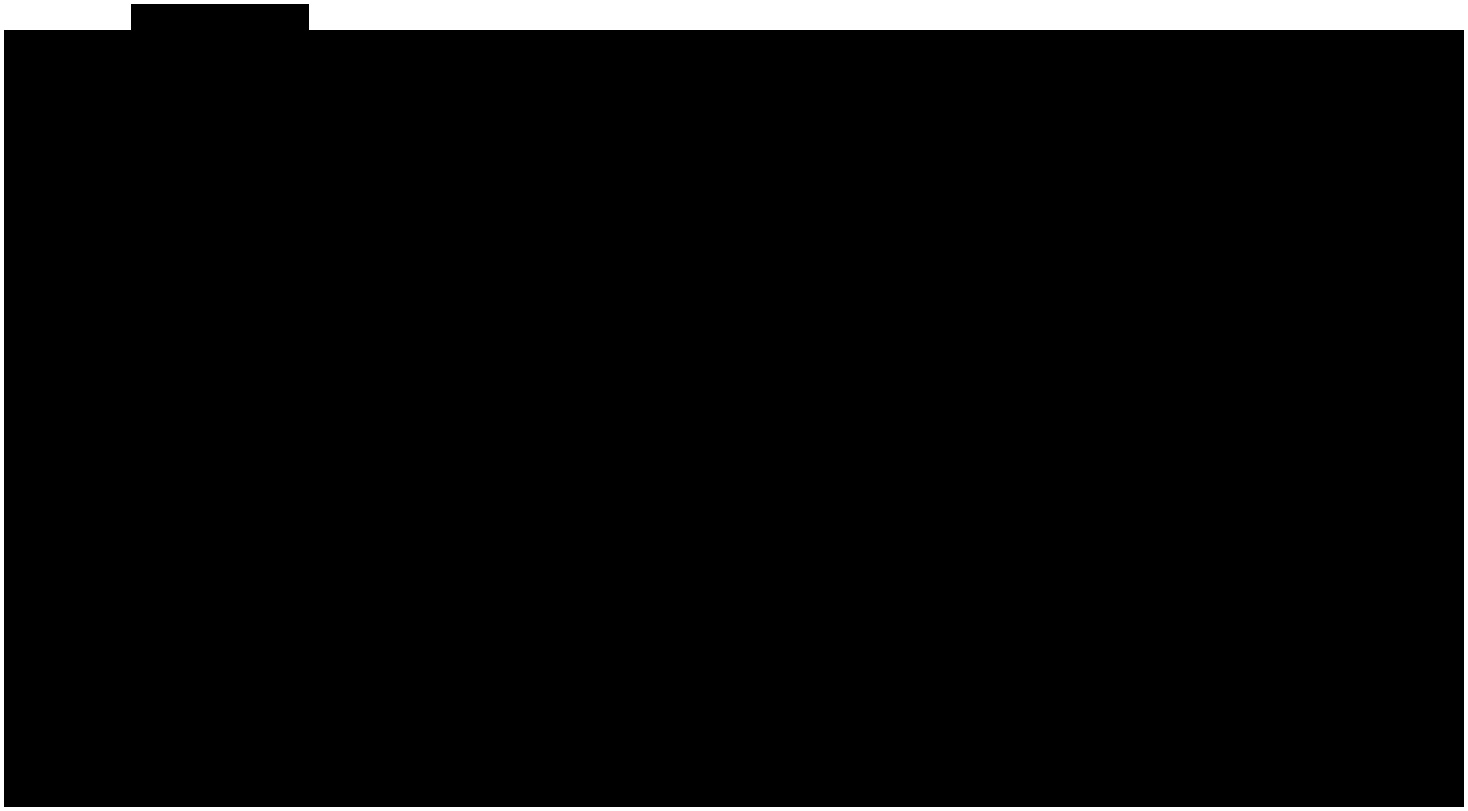
11 STATISTICAL ANALYSIS AND DATA MANAGEMENT

11.1 SAMPLE SIZE CALCULATION

Two previous studies [10, 11] assessed differences in corneal response to 3-hour closed eye CL wear between low Dk/t HEMA and PMMA lenses in a group of neophytes. However, there is no

data from similar methodology and participant groups on which to calculate the sample size in the current study. A guide to the minimum sample size for Visit 2 bulbar and limbal hyperemia measures has been calculated from hyperemia data reported in a recent publication reporting objective bulbar and limbal hyperemia (using Oculus Keratograph) while wearing DDH contact lenses in habitual silicone hydrogel lens wearers.[16] This data indicates that to detect an effect size of 1.2 (or 0.5 grade difference) in either bulbar or limbal hyperemia with power of 0.9 and alpha level 0.05, a minimum total sample size of 32 participants should be studied for the 2 study groups in Day 2 (Figure 1).

In this initial study to evaluate the response differences between groups it is proposed that 17 participants in each group (shown in randomized side of the graph) are studied to evaluate the size of the differences in bulbar and limbal hyperemia between groups found following lens removal and across the recovery period at each time point. If the data shows a trend of finding a difference between groups, this data can be used to plan a larger study which is powered



11.2 STATISTICAL ANALYSIS

All data will be analyzed by CORE at the University of Waterloo. 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.). 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.

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 and complete all scheduled study visits will be included in the analysis cohort. In the event of missing data, individual data points will be excluded from 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 review will be led by the lead investigator at each site and 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 each 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 SPONSOR RESPONSIBILITIES

The Sponsor has the ultimate responsibility for monitoring. The Sponsor is to supply and keep an up-to-date signed protocol and protocol amendments, and provide devices which are the subject of the clinical investigation.

The sponsor should ensure: appropriate information is provided to the Investigators to conduct the study; that deviations are reviewed with the Investigator as needed and included in the final report. Adverse events are reported by the Investigator, and the sponsor in turn will then notify their applicable regulatory authorities, and other investigators as appropriate. The Sponsor is to maintain Sponsor-specific study documentation as required by the regulatory authorities and to ensure the Investigator is aware of their record keeping responsibilities.

12.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring participant safety and data quality by: protocol compliance, adherence to GCP and local regulatory requirements, and the Declaration of Helsinki. The Investigator should be appropriately qualified and legally entitled to practice, and be trained in the proper method of obtaining informed consent.

The Investigator must have the appropriate resources to conduct the study, be familiar with the protocol and agree to adhere to it, support monitoring and auditing activities, communicate with the Sponsor regarding any study issues or need for protocol modifications, make the necessary arrangements to ensure proper conduct and completion of the study, and ensure the protection and welfare of the participant, including arranging any emergency treatment as needed.

The Investigator must ensure written ORE approval for the study site is received prior to the start of the study, that the respective ORE and Sponsor is kept informed of the study progress, including adverse events and deviations as required by them, and that any changes to the protocol are notified to the ORE and review written approval prior to implementation.

12.4 RECORD KEEPING

Detailed records of all study visits will be made using the Case Report Forms (CRFs). Each subject will be identified on the CRFs with a study ID number which will not contain any identifying information such as initials and date of birth. 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.

12.5 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 guidelines set forth in the general work agreement with the site. The CRFs in the external study site will be scanned and electronically transferred via the University of Waterloo Secure File Transfer Service to CORE for data entry. The Sponsor will be notified and consulted if ever the files are to be destroyed. Copies of raw data 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 at CORE and the relevant part of the study data will be retained for a minimum of 20 years at Eurolens Research study site.

12.6 DATA ENTRY / DATA MANAGEMENT

Data will be entered into an electronic spreadsheet at CORE. 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 CORE 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 pre-defined comments will be entered into the study database. Only relevant and applicable comments will be included in the final report as deemed necessary by the lead investigator.

13 PROTOCOL TRAINING

All study personnel will be required to complete training prior to their involvement in the study. Records of training will be kept at the study site.

14 STUDY MONITORING

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

Status reports will include:

- The number of participants screened, enrolled, and randomized (i.e. assigned a study ID number), discontinued and completed.
- Details of protocol deviations.
- Reports of unintended events.

Study monitoring visits may be conducted throughout the study and, if so, would be scheduled by the study sponsor in conjunction with the site. In addition study records may be inspected at the study site 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 study site.

Each study site will conduct internal monitoring of proper consent documentation and reporting of protocol deviations and adverse events.

15 STUDY MANAGEMENT

15.1 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.

15.1.1 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations may impact the research protocol, information consent document 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 respective Office of Research Ethics (ORE) at each site:

- Changes in procedures initiated to eliminate immediate risks/hazards to participants;
- Enrollment of participants outside the protocol inclusion/exclusion criteria whether agreed to or not by the sponsor;
- 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;
- Information consent documentation violations: no documentation of informed consent; incorrect version of, or incomplete, informed consent documentation used.

15.1.2 MINOR PROTOCOL DEVIATIONS

Protocol deviations caused by or which originate with research participants are considered minor, and normally are not reported to the ORE nor to the Sponsor (other than within the study report) unless these result in increased risk to the participant(s) or potentially affect data

integrity. The following are examples of protocol deviations that are considered minor and do not require reporting to the ORE:

- Logistical or administrative aspects of the study (e.g., study participant missed appointment, change in appointment date);
- 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).

15.1.3 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 participants or others must be reported to the Sponsor and to the respective ORE within 7 days for CORE (or as per guidelines of the respective ORE for each study site), using the ORE Protocol Deviation Report Form (PDRF). Information from the PDRF is provided to the Clinical Research Ethics Committee (CREC) at the next monthly meeting. The PDRF requirements indicated above are only applicable to CORE. Eurolens Research study site will follow their local ethics committee requirements for reporting protocol deviations to the respective ethics committee.

All protocol deviations (major and minor) occurring during the study will be documented and included in the final report.

15.2 PREMATURE TERMINATION OF THE STUDY

The sponsor, study sites or the Office of Research Ethics for the study site may terminate the study at any time for any reason.

15.3 STUDY PARTICIPANT RECORDS

Study participant records will be completed to comply with GCP guidelines. Records will contain:

- Unique study acronym and/or code;
- Participant ID;
- Date enrolled;
- Confirmation by investigator that participant met eligibility criteria;
- Confirmation that participant received a signed and dated copy of informed consent;
- Exit date;
- Investigator's signature confirming each participant's study exit.

15.4 RETENTION OF STUDY RECORDS AND DATA

Records and data from this study will be retained for a minimum of 25 years at CORE and 20 years at Eurolens Research, respectively. Details regarding storage procedures are given in SOPs of the respective site.

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 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 required as a consequence of study participation will be paid to the participant by the study site, which will then claim from the sponsor (bills and prescription receipts provided). The participant must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

19 REPORT

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