® £2 u [redacted]

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

Centre for Ocular Research & Education (CORE)

School of Optometry & V1s1on SCience IUn1vers1ty of Waterloo. 200 un,vers1ty Avenue West I Waterbo. ON. Canada N2L 3Gl
+1 (519) 888-47421 CORE uwaterloo.ca

Protocol

A BILATERAL DISPENSING COMPARISON OF BIOFINITY TORIC AND ULTRA FOR ASTIGMATISM (PIAN0-2)

Sponsor Company	CooperVision, Inc.
Sponsor Study number:	EX-MKTG-91
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Document Type:	Study protocol
Clinical Site:	CORE, University of Waterloo

	Reviewed and approved, name & signature	Date *ddlmmmf*
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

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

A BILATERAL DISPENSING COMPARISON OF BIOFINITY TORIC AND ULTRA FOR ASTIGMATISM (PIANO-2)

Sponsor Company	CooperVision, Inc.
Sponsor Study number:	EX-MKTG-91
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Document Type:	Study protocol
Clinical Site:	CORE, University of Waterloo

This protocol remains the exclusive property of the CORE until it is commissioned by the sponsors.

	Reviewed and approved, name & signature	**Date** dd/mmm/yyyy
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	

[redacted]

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

DOCUMENT CHANGE HISTORY

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

Table of contents

Confidentiality

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

CooperVision is evaluating the subjective acceptance of BiofinityToric (CooperVision) in comparison with Ultra for Astigmatism (Bausch & Lomb), when each lens is worn on a daily wear basis over one (1) month in a randomized bilateral, cross-over, dispensing study.

2 OBJECTIVES

The objective of the study is to evaluate the subjective acceptance of Biofinity Toric test lens when worn on a daily wear modality over 1 month.

The primary study measures are:

- Comfort subjective ratings (0-10 scale) and lens preference with respect to comfort (5-step Likert)
- Dryness subjective ratings (0-10 scale) and lens preference with respect to dryness (5-step Likert)

The secondary study measures are:

- [redacted]Handling subjective ratings (0-10 scale)

[redacted]

- [redacted]

3 HYPOTHESIS

The study hypothesis is that Biofinity Toric (BT) 'test lens' will have equal or better subjective acceptance by wearers than the 'control lens', Ultra for Astigmatism (UT).

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This study is a prospective, double-masked (investigator and participant), bilateral, randomized, cross-over dispensing study comparing subject acceptance of BT test lens against UT control lens. [redacted] Both test and control lenses will be used in their approved daily lens wear modality for approximately one (1) month. It is anticipated that this study will involve up to 5 scheduled visits:

Visit 1: Includes screening, baseline assessments, fitting of both lens types.

Visit 2: Dispense lens pair #1 (either test or control lens).

Visit 3: 1-month follow-up visit of lens pair #1

Visit 4: Dispense of lens pair #2 (either test or control lens)

Visit 5: 1-month follow-up visit of lens pair #2 and study exit.

The study design in shown in Figure 1.

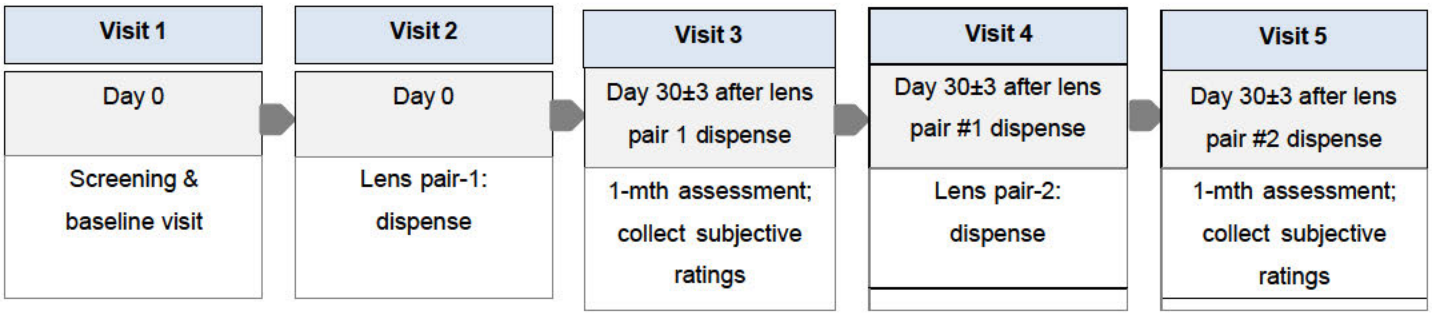

Figure 1: Study Design

4.1.2 RANDOMIZATION

A randomization schedule will be generated using SAS or a web-based program: (www.randomization.com). An example of the format generated is given in Appendix 23. The final study randomization schedule will be generated by the CORE Data Management Team, and provided to the research assistants for use during the study. Study investigators will remain masked to the randomization schedule until the study is completed and the database is locked.

4.1.3 MASKING

Participants will be masked to lens assignment. Lenses will be dispensed to participants in a manner to maintain subject masking as described in Section 4.7.4. Investigators will be masked as much as possible. [redacted]

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

4.4 CLINICAL TRIAL REGISTRATION

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

4.5 INFORMED CONSENT

Informed consent shall be obtained in writing from all participants prior to their enrolment in the study (Appendix 1), and before any procedure specific to the clinical investigation is carried out.

4.6 STUDY POPULATION

4.6.1 NUMBER OF PARTICIPANTS

Up to 30 participants will be dispensed / randomized with study products, with a target of 26 completing the study. Participants will be recruited using CORE records and advertising approved by the UW Office of Research Ethics (Appendices 2, 3a, and 3b). 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.

4.6.2 INCLUSION AND EXCLUSION CRITERIA

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

1. Is at least 17 years of age 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. Is an adapted soft contact lens wearer, who currently wears contact lenses for a minimum 3 days/week and 8 hours/day AND who anticipates no difficulty wearing CLs for 6 days/week, 10 hours /day.
6. Is willing to wear contact lens in both eyes for the duration of the study;
7. Has a minimum astigmatism of - 0.75, determined by refraction;
8. Can be fit with the two study contact lens types in the powers available;
9. Has a distance visual acuity of 0.20 logMAR (approx 20/30) or better, determined by refraction;
10. Can achieve a distance visual acuity of 0.20 logMAR (approx 20/30) or better in each eye with the study contact lenses.
11. Has clear corneas and no active* ocular disease;

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

1. Is participating in any concurrent clinical trial;
2. Has any known active* ocular disease and/or infection;
3. Has a systemic condition that in the opinion of the investigator may affect a study measure;
4. Is using any systemic or topical medications that in the opinion of the investigator may affect a study measure;
5. Has known sensitivity to fluorescein dye or products to be used in the study;
6. 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;
7. Is pregnant, lactating or planning a pregnancy at the time of enrolment (by verbal confirmation at the screening visit);

8. Is aphakic;
9. Has undergone refractive error surgery.
10. Has participated in the PIANO (i.e. EX-MKTG-83) Study.

* 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.

4.6.3 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.

4.7 STUDY MATERIALS

4.7.1 LENSES

Details of study lenses are show in Table 1.

Table 1: Lens parameters to be used in this study

	Biofinity Toric	**Ultra for Astigmatism**
Manufacturer	CooperVision Inc.	Bausch & Lomb
Material	comfilcon A	samfilcon A

	Biofinity Toric	Ultra for Astigmatism
Health Canada license #	70149	94501
EWC (%)	48%	46%
Dk/t (-3.00D)	116.0	114.0
BOZR (mm)	8.7	8.6
Diameter (mm)	14.5	14.5
Sphere power (D)	+6.00 to -6.00D (0.25 steps) +6.00 to +8.00 and -6.00 to -10.00 (0.50 steps)	+6.00 to -6.00D (0.25 steps) +6.00 to +8.00 and -6.00 to -10.00 (0.50 steps)
Cylindrical Power (D)	-0.75 to -2.25 (0.50 steps)	-0.75 to -2.25 (0.50 steps)
Axis (degree)	10° to 180° (10° steps)	10° to 180° (10° steps)

4.7.2 CONTACT LENS CARE SYSTEM

Alcon Optifree PureMoist solution (rub and rinse) will be used as the contact lens care system in this study.

4.7.3 REWETTING DROPS

Participants will not be encouraged to use rewetting drops; however, those who habitually use rewetting drops will be allowed to continue using their normal drops. Rewetting drop use will be recorded at each visit. In the event of an adverse event, rewetting drops may be given to participants.

4.7.4 CONTACT LENS DISPENSING

The lenses will be provided to the participant after being transferred, complete with blister pack solution, to a contact lens cup; this will maintain participant masking and aid investigator masking. The use of saline for rinsing the contact lens prior to insertion is permitted if necessary. Saline will not be dispensed during the study.

4.7.5 ORDERING CONSUMABLES

A stock of both study lenses will be provided by the Sponsor.

CORE will source the care solution.

CORE must maintain an accurate accounting of the study product during the study. A detailed inventory must be completed for all study supplies.

4.7.6 DISPOSING OF CONSUMABLES

This study provides consumables (lenses and lens care solution) to participants for use during the study. Worn lenses will be collected from the participants at each 1-month visit (or on discontinuation/exit from the study) and at the end of the study they will be disposed of according to UW guidelines, unless otherwise directed by the study Sponsor. Worn lenses specifically associated with adverse events/product observations may be retained either at CORE or returned to CooperVision. Typical analysis in these cases relates to inspection for damage and/ or bacterial contamination.

4.7.7 PRODUCT ACCOUNTABILITY

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

4.8 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 5 scheduled study visits, including:

- Visit 1: Includes screening, baseline and fitting of both study lenses
- Visit 2: Dispense of lens pair #1 (If appropriate can be combined with visit 1)
- Visit 3: 1-month follow-up visit of lens pair #1 (30±3 days after dispense)
- Visit 4: Dispense of lens pair #2 (is normally combined with visit 3)
- Visit 5: 1-month follow-up visit for lens pair #2 (30±3 days after dispense) and study exit.

A scheduled follow-up visit may only take place when the participant attends wearing the study lenses for at least four hours. If this is not the case and the participant is not experiencing any problems with the lenses, the appointment will be rescheduled, ideally within the visit window.

Visits that fall outside of the specified visit windows will be designated as protocol deviations and at the end of the study the data collected will be assessed for its suitability to be included in the analysis population.

4.8.1 STUDY VISITS

The summary of visit codes is shown in Table 2.

Table 2: Summary of visit codes

Visit #	Visit code	Visits

Visit 1	V1 (V1-R1,& V1-R2 for re-screening if required)	Screening, baseline & fit of both study lens (day 0)
Visit 2	V2	Dispense lens pair #1 (day 0)
Visit 3	V3	1-month follow-up of pair #1 (30±3 days after dispense of pair #1)
Visit 4	V4	Dispense lens pair #2
Visit 5	V5	1-month follow-up of pair #2 (30±3 days after dispense of pair #2)
Exit Visit	any	Study exit

4.8.2 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 are outlined below:

The participant is expected to attend the screening / baseline visit not wearing their habitual contact lens products, instead wearing their spectacles.

The participant will be required to read and sign an Informed Consent Form (Appendix 1) 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)

[redacted]

The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion criteria and exclusion criteria and is eligible to continue in the study.

Trial fitting of both study lenses will be done:

- [redacted]
- The contact lenses will be provided to participants in a manner which does not unmask the participant, as described in Section 4.7.4.
- The lenses will be inserted by the participant.

[redacted]

- [redacted]

4.8.3 DISPENSING LENS PAIR #1

The participant will be assigned a randomization ID and the first pair (lens pair #1) of contact lenses (either test or control lens) will be selected according to the randomization table.

Lens pair #1 will be provided to participants in a manner which does not unmask the participant or investigator, as described in Section 4.7.4.

The lenses will be inserted by the participant.

The contact lenses will be allowed to settle for 10 minutes.

The participant will be asked to give subjective [redacted]_ratings (Appendix 9) for:

a) Comfort at insertion (0-10 scale)
[redacted]
c) [redacted]
d) Ease of insertion (0-10 scale)
[redacted]

[redacted]

[redacted]

- Participant will be provided with the contact lens care solution, lens case, and lens care instruction.
- [redacted]

4.8.4 1-MONTH FOLLOW-UP OF PAIR #1

Participants will be asked to wear lenses for at least 4 hours prior to the visit appointment. Participants who attend without lenses in-situ (wearing lenses) for at least four hours will be rescheduled (unless they report problems when wearing the lenses).

[redacted]

- The participant will be asked to score their subjective responses by reflecting on a typical day during the previous week of lens wear, [redacted] includes the following:
  - [redacted]
  - Overall comfort (0-10 scale)
  - Overall dryness (0-10 scale)
  - Ease of insertion (0-10 scale)
  - Ease of removal (0-10 scale)

[redacted]

[redacted]

The lenses will be removed. Lens disposal procedures are detailed in Section 4.7.6.

[redacted]

4.8.5 DISPENSING LENS PAIR #2

The participant will be assigned the second pair (lens pair #2) of contact lenses (either test or control lens) will be selected according to the randomization table.

Lens pair #2 will be provided to participants in a manner which does not unmask the participant or investigator, as described in Section 4.7.4.

The lenses will be inserted by the participant.

The contact lenses will be allowed to settle for 10 minutes.

The participant will be asked to give subjective [redacted]_ratings (Appendix 9) for:

g) Comfort at insertion (0-10 scale)
[redacted]

j) Ease of insertion (0-10 scale)
[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

- Participant will be provided with more contact lens care solution, new lens case, and lens care verbal re-instruction.
- The participant will be reminded to bring back [redacted] the remaining lens care solution and lens case to the next visit, 1-month visit of lens pair #2.

4.8.6 1-MONTH FOLLOW-UP OF PAIR #2 & STUDY EXIT

Participants will be asked to wear lenses for at least 4 hours prior to the visit appointment. Participants who attend without lenses in-situ (wearing lenses) for at least four hours will be rescheduled (unless they report problems when wearing the lenses).

- [redacted].
- The participant will be asked to score their subjective responses and indicate any preference between the two lens types by reflecting on a typical day during the previous week of lens wear, as detailed in the subjective ratings form [redacted] and includes the following:

  [redacted]

  - Overall comfort (0-10 scale)
  - Overall dryness (0-10 scale)
  - Ease of insertion (0-10 scale)
  - Ease of removal (0-10 scale)

  [redacted]

  - [redacted]

[redacted]

[redacted]

  [redacted]

  [redacted]

  [redacted]

  [redacted]

[redacted]

The lenses will be removed. The disposal procedures are detailed in Section 4.7.6.

[redacted]

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.

4.8.7 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.

4.9 SUMMARY OF STUDY PROCEDURES

Table 3 summarizes the visits and procedures for the study.

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

	V1 Screen & fit	V2 Disp Pr1	2Wk home rating Pr1	V3 1-month progress Pr1	V4 Disp Pr2	2Wk home rating Pr2	V5 1-month progress Pr2	V-Exit
Consent process	x							
CL history and wear schedule	x	x		x	x		x	
Health & medication	x	x		x	x		x	
[redacted]	x							

	V1 Screen & fit	V2 Disp Pr1	2Wk home rating Pr1	V3 1-month progress Pr1	V4 Disp Pr2	2Wk home rating Pr2	V5 1-month progress Pr2	V-Exit
[redacted]								
[redacted]	x							
[redacted]	x							
Study lens optimised fitting (both lens types)	x							
Dispense study CLs*		x			x			
[redacted]	x	x		x	x		x	
Spherical over-refraction with study CLs (if applicable)	x	x		x	x		x	
[redacted]	x	x		x	x		x	
Complete subjective rating in office		x		x	x		x	
[redacted]			x			x		
[redacted]				x			x	
[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.

[redacted]

[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 CORE. 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 University of Waterloo's 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 a minimal risk study because of the use of marketed products and standard optometric assessments.

Contact lenses in this study will be worn on a daily wear basis. 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. 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.

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, there is a significantly increased risk of an adverse reaction compared with wearing contact lenses on a daily wear basis.

Additionally, it is possible that participants may experience 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 and foreign body sensation.

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.

This study may help the study sponsor to better understand the performance of the products being used in this study.

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 SOP012_v01 for a description of adverse events, including management and reporting (Appendix 26).

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: Notify sponsor as soon as possible, **within 24 hours;** ORE reporting will be **within 24 hours** 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**; ORE
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)	reporting as per requirements
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

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.

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 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.

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 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 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).

Sponsor contact details are:

[redacted]

8 DISCONTINUATION FROM THE STUDY

[redacted] 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 4.6.2.
- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort and /or vision 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, CORE or the Office of Research Ethics at the University of Waterloo.

A discontinuation form (Appendix 12) 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 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).

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

10 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit a study completion form (Appendix 13) 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 (Appendix 15).

Once their involvement in the study is complete, participants will be informed about receiving feedback following study completion in the Letter of Appreciation (Appendix15).

[redacted]

11 STATISTICAL ANALYSIS AND DATA MANAGEMENT

11.1 SAMPLE SIZE CALCULATION

Sample size was calculated using the mean comfort rating data from the previous pilot PIANO study (EX-MKTG-83). The data from the PIANO-2 will be pooled with data from the pilot PIANO study, therefore anyone who participated in the pilot study will be excluded from participating in the PIANO-2 study.

A total sample size of 44 is recommended to provide a minimum power of 90 with an alpha of 0.05 in a two-tailed t-test to detect a difference of 1 comfort unit (scale of 0-10). Based on the results from the pilot study (i.e. PIANO Study) the sample size needed for PIANO-2 will be aimed at 26 to complete (i.e. total of 44 minus the 18 completed participants from the pilot study). Therefore, it is recommended that at least 30 subjects are dispensed in the PIANO-2 study, with a target of 26 to complete.

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.

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.

Table 4 lists the primary study measures and anticipated statistical procedures.

Table 4: Study measures and anticipated statistical procedures

Variable	Analysis	Statistical test
Analogue scales/Numeric scales/Preference scales/VA Lens parameters Biomicroscopy (continuous variables)	*Effect of lens type*	RMANOVA/MANOVA/ Friedman /Wilcoxon matched pairs test Tukey HSD post hocs Paired t-test Chi-square test
Biomicroscopy (ordinal variables)	*Effect of lens type*	Friedman Wilcoxon matched pairs test
Analogue scales/Numeric scales/Lens parameters, Biomicroscopy (continuous)	*Relationship between slit lamp findings and analogue scales*	Pearson correlation - r
Biomicroscopy (ordinal variables)	*Relationship between slit lamp findings and analogue scales*	Spearman correlation - rho

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 will 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 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 is received prior to the start of the study, that the 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). 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 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.

12.6 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. The investigator will review the take home questionnaires with the participant. 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 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 CORE.

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 will be scheduled by the study sponsor in conjunction with the lead investigator. In addition study records may be inspected at CORE 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 CORE.

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 University of Waterloo's Office of Research Ethics (ORE):

- 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 PROTCOL 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 ORE within 7 days (as per guidelines of the ORE), using the Protocol Deviation Report Form 107 (PDRF). Information from the PDRF is provided to the Clinical Research Ethics Committee (CREC) at the next monthly meeting.

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, CORE or the Office of Research Ethics at the University of Waterloo 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. Details regarding storage procedures are given in the CORE SOP.

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 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.

19 REPORT

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

[redacted]