CORE
Centre for Ocular Research & Education

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

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Protocol

THE EFFECT OF XIIDRA ON COMFORT AND DRYNESS IN SYMPTOMATIC CONTACT LENS WEARERS (COLLIE)

Sponsor: CORE (IIR funded by Novartis)

Funding agency study number [redacted]

CORE protocol number: P/662/19/SR

Protocol author: [redacted]

Principal investigator(s): Dr Lyndon Jones

Role & printed name	Reviewed and approved (sign)	Date DD/MMM/YYYY
Principal investigator: [redacted]	[redacted]	
Qualified Investigator: [redacted]		
Lead investigator: [redacted]		
Protocol author: [redacted]		
Quality assurance: [redacted]		
Sponsor: [redacted]		

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Quality assurance: [redacted]		
Sponsor:	n/a	

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DOCUMENT CHANGE HISTORY

Version date	Author	Description of change(s)
1.0	[redacted]	Original protocol
2.0	[redacted]	Change of funding source from Shire/Takeda to Novartis; corrected error on page 1 re CORE protocol # and author
3.0	[redacted]	Change to 7 Adverse Event section to meet Novartis regulatory requirements

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Confidentiality

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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

The Tear Film and Ocular Surface Society's (TFOS) workshop on contact lens discomfort (CLD) has defined CLD as "a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear".[1]

Contact lens discomfort is the leading cause for CL "dropout", is prevalent in up to 50% of current wearers and is typically associated with symptoms of ocular dryness.[2] To alleviate these symptoms, CL wearers use various strategies, including reducing wear time (reducing days per week and/or hours per day) and adopting the use of rewetting drops. While using rewetting drops may provide temporary relief, their use was rated to be of moderate benefit only, particularly later in the day.[2]

The association between CL wear and inflammatory markers in the tear film has also been investigated in the past. Schultz and Kunert reported significantly higher levels of the cytokine IL-6 in contact lens wearers compared to non-lens wearers, with IL-6 levels in the same participants reducing to non-detectable levels after CL wear had been prohibited for six days.[3]

Xiidra (lifitegrast 5.0% ophthalmic solution) has been recently approved by Health Canada as a treatment for both signs and symptoms of dry eye disease. Xiidra has been shown to be effective in relieving dryness symptoms in subjectively rated ocular dryness (Eye dryness score; Visual analogue scale from 0 (no discomfort) to 100 (maximum discomfort)) after two, six and 12 weeks of use compared to a vehicle control.[4,5] A recent study has found improved comfort in wearers of the B&L Ultra contact lens type, a low-modulus, nonionic, monthly replacement silicone hydrogel contact lens.[6] These findings suggest that using Xiidra may also be of benefit for symptomatic CL wearers of other lens types who experience ocular dryness and discomfort.

The purpose of this study to evaluate changes in comfort and dryness in symptomatic contact lens (CL) wearers after using Xiidra (lifitegrast 5.0% ophthalmic solution) for 12 weeks.

2 OBJECTIVES

The primary objective is to investigate whether comfort and dryness in symptomatic contact lens (CL) wearers improve after using Xiidra (lifitegrast 5.0% ophthalmic solution) for 12 weeks. In addition, this study will also evaluate whether the quantity of tear film inflammatory markers changes after use of Xiidra for 12 weeks.

The primary outcome variables for this study are subjective ratings of 'CL-related discomfort and dryness', as part of the visual analog scale (VAS) for symptom assessment, at 12 weeks compared to baseline.

Other outcome variables for this study include:

- Subjective ratings of CL-related discomfort and dryness, as part of the visual analog scale (VAS) for symptom assessment, at two and six weeks compared to baseline;
- CLDEQ-8 score at two, six and 12 weeks compared to baseline;
- Quantity of tear film inflammatory markers after 6 hours of CL wear at two, six and 12 weeks compared to baseline
    - Inflammatory markers for 10 cytokines will be evaluated using the MSD (MesoScale Discovery) platform. The Proinflammatory Panel 1 (human) Kit will be used; it provides assay-specific components for the quantitative determination of IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α.
- Ocular redness at two, six and 12 weeks compared to baseline;
- Non-invasive tear break-up time (pre-lens; PLNITBUT) at two, six and 12 weeks compared to baseline.

3 HYPOTHESIS

The primary hypothesis is that symptomatic CL wearers exhibit reduced levels of dryness and discomfort after 12 weeks of Xiidra use compared to baseline.

4 MATERIALS AND METHODS

4.1 STUDY DESIGN

4.1.1 OVERALL DESIGN

This is a prospective, open-label, dispensing pilot study with five study visits over the course of 12 weeks. The protocol will be submitted to a University of Waterloo Research Ethics Committee for approval. The study will be designed to be in conformance with the ethical principles in the Declaration of Helsinki, with the ICH guidelines for Good Clinical Practice (GCP), with the University of Waterloo's Guidelines for Research with Human Participants and with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition. A flow chart of the study design is shown in Figure 1.

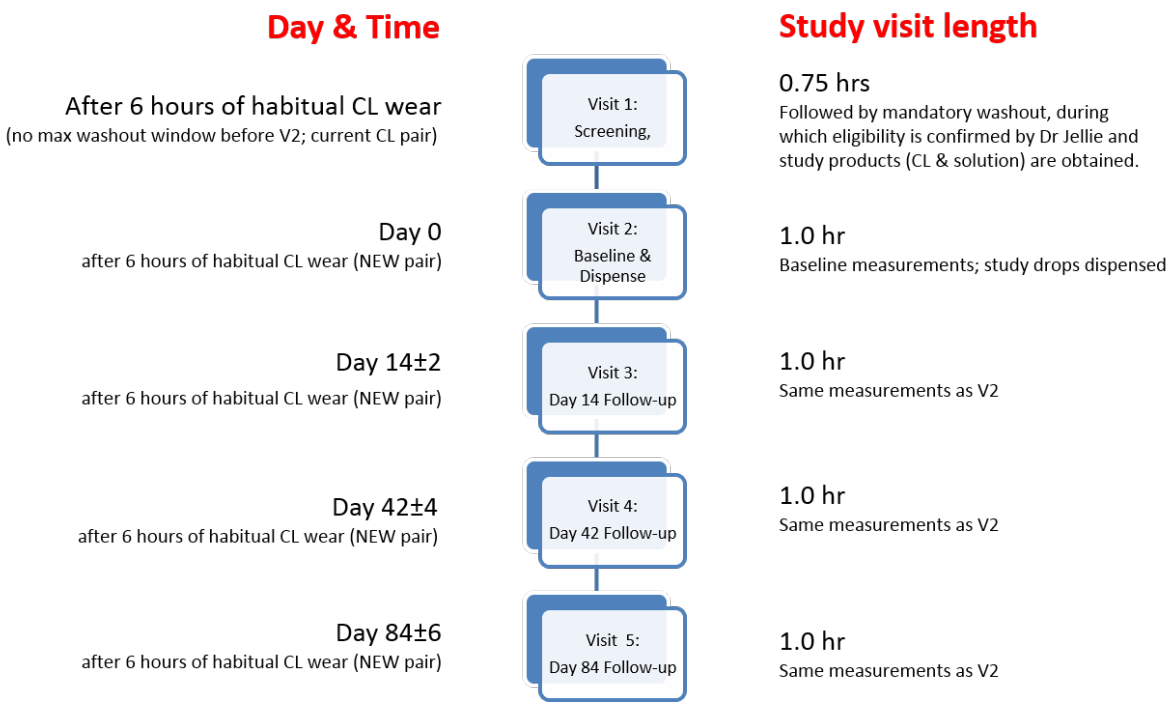

Figure 1: Study flow chart

4.1.2 RANDOMIZATION

There is no randomization in this study. Each participant will use the same study drops, Xiidra, over the course of the 12 week study.

4.1.3 MASKING

This is an open-label study that will not involve masking. Each participant will use the same study drops, Xiidra, over the course of the 12 week study.

4.2 STUDY POPULATION

4.2.1 SAMPLE SIZE CALCULATION

This is a pilot study. As no data on contact lens wearers using Xiidra are available yet, a number of 40 symptomatic wearers has been estimated as sufficiently large to detect differences in comfort ratings at 12 weeks compared to baseline. The data collected in this pilot study may be used to calculate sample size for future studies.

4.2.2 NUMBER OF PARTICIPANTS

Participants will be recruited using CORE records and advertising approved by the UW Office of Research Ethics. Up to 55 eligible participants may be dispensed with study products, with a target of 40 participants completing the study. Informed consent will be obtained for all participants prior to their enrolment in the study (Appendix 1).

4.2.3 INCLUSION AND EXCLUSION CRITERIA

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

1. Is at least 18 years of age and has full legal capacity to volunteer;
2. Has read and signed an information consent letter;
3. Is willing and able to follow instructions and maintain the appointment schedule;
4. Currently wears daily, soft, frequent replacement lenses (daily, bi-weekly or monthly disposable lenses) in both eyes, that are available in Canada, for a minimum of 5 days/week for 6 hours/day over the last month, and is willing to continue to do so during the study;
5. Is a symptomatic CL wearer as determined by Eye Dryness Score[4,5] (EDS) ≥40 at the end of the wear day AND according to the classification by Young et al[7];
6. Can achieve acceptable lens fit as well as visual acuity (VA) correctable to logMAR +0.20 or better in each eye with their habitual contact lens type;
7. Has a history of artificial tear or rewetting drop use at least once in the last 30 days;
8. Is willing to use the Xiidra study drops twice a day on a daily basis (irrespective of CL wear) and to stop use of any habitual rewetting drops and/or artificial tears over the course of the 12-week treatment phase;

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

1. Is participating in any concurrent clinical or research study;
2. Is wearing soft CLs on an extended wear basis (i.e. overnight) or is a rigid gas permeable lens or hybrid lens wearer;
3. Has a known sensitivity to the investigational product or diagnostic substances (e.g. fluorescein) to be used in the study;
4. Has any known ocular disease and/or infection, that's either currently active* or has occurred within the previous 30 days;
5. Has a systemic condition that in the opinion of the investigator may affect a study outcome variable (examples may include active or uncontrolled systemic conditions such as allergies, autoimmune disease or immunodeficiency disease);
6. Is using any systemic or topical medications that in the opinion of the investigator may affect a study outcome variable, including but not limited to topical cyclosporine, any other topical ophthalmic medication, antihistamines, and aspirin;
7. Is pregnant, lactating or planning a pregnancy at the time of enrolment (by self-report);**
8. Has undergone refractive error surgery such as LASIK within the last 12 months;

9. Has a history of yttrium-aluminium-garnet laser posterior capsulotomy within the previous 6 months,
10. Is an employee of the Centre for Ocular Research & Education;

* 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.

** The reason for excluding pregnant or nursing participants is based on recommendations from the Xiidra product monograph[8]:

"Pregnant Women

There are no adequate and well-controlled studies of Xiidra use in pregnant women. In a reproductive toxicology study in rats, intravenous administration of lifitegrast from pre-mating through gestation day 17 resulted in an increase in incidence of pre-implantation loss and incidences of skeletal malformations. In a reproductive toxicity study in rabbits, intravenous administration of lifitegrast during organogenesis resulted in incidences of omphalocele. Since human systemic exposure to lifitegrast following ocular administration at the recommended human ophthalmic dose (RHOD) is low, the applicability of animal findings to the risk of lifitegrast use in humans during pregnancy is unclear.

Xiidra should be used with caution during pregnancy (see TOXICOLOGY, Reproductive and Developmental Toxicity).

Nursing Women

It is not known whether Xiidra is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Xiidra is administered to a nursing woman."

4.2.4 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 conjuunctival staining, scars etc.)

The maximum total number of screenings permitted will be 2, 1 initial screening and 1 potential re-screening.

4.3 STUDY MATERIALS

4.3.1 CONTACT LENSES AND SOLUTIONS

Study participants will be wearing their habitual contact lens type/ brand throughout the study and will continue to use their habitual lens care if required. Participants will be instructed to wear their contact lenses for a minimum of 5 days/ week, 6 hours/day throughout the study. Participants will also be instructed to wear a new pair of lenses at each visit except for the Screening visit, at which a lens of any age (e.g. fresh daily disposable, reusable in the middle or at end of cycle).

Participants will be instructed to bring their care system (if applicable) and an unopened package of their current contact lenses to the screening visit. The specifications of the contact lenses and care system will be noted.

Participants will be supplied with contact lenses and lens care solutions (as applicable) throughout the study. Participants will also be supplied with spare contact lenses to cover the number of lenses used by the participant throughout the screening period between V1 and V2. The number of CLs to be replaced depends on the replacement modality, and will be calculated accordingly.

4.3.2 STUDY DROPS

Participants will be provided with sufficient supplies of Xiidra (lifitegrast ophthalmic solution 5.0%) for the 12-week treatment phase. Study drops will be dispensed at the dispense visit (V2), with additional drops being provided at each follow-up visit (except for the last study visit, V5) to last until the next visit.

4.3.2.1 STUDY DROP DETAILS[8]

Xiidra (lifitegrast ophthalmic solution 5%) is supplied as a sterile solution with a pH range of 7.0 – 8.0 and an osmolality range of 200 – 330 mOsmol/kg.

Xiidra contains the following ingredients:

Active: lifitegrast 50 mg/mL;

Inactives: sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH), sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, and water for injection.

DIN (Health Canada): 02471027

Xiidra is a sterile, preservative-free, clear, colourless to slightly yellowish solution supplied in low density polyethylene single-use containers, packaged in foil pouches. Each single-use container contains 0.2 mL solution corresponding to 10 mg lifitegrast.

4.3.2.2 ADMINISTRATION[8]

Participants will be asked to use the Xiidra drops twice daily, approximately 12 hours apart, as per manufacturer's guidelines (available at http://www.shirecontent.com/PI/PDFs/Xiidra_USA_ENG.pdf). Participants are asked to use the drops every day, even if they don't intend to wear their contact lenses on that day. On days when contact lenses are intended to be worn, instillation of Xiidra must be **at least 15 minutes prior to insertion of CL**, with the second daily dose to be applied **after removal of the CLs.** Xiidra drops are not to be instilled while contact lenses are on the eyes.

Study participants will be advised that

- the solution for one single-use container is to be used immediately after opening;
- it can be used to dose both eyes;
- the single-use container, including any remaining contents, should be discarded immediately after administration.

4.3.3 REWETTING DROPS

Participants who habitually use rewetting drops will be permitted to continue using these up until the day before the V2 visit day, i.e. until the day before they will be dispensed the Xiidra study drops. During the course of the 12-week study, participants will be prohibited from using any other kind of rewetting drops or artificial tears other than the Xiidra study drops.

4.3.4 ORDERING CONSUMABLES

CORE will order contact lenses and contact lens care systems (as applicable) for each participant. The funding agency, Novartis, will provide the Xiidra eye drops.

4.3.5 DISPOSING OF CONSUMABLES

Unused Xiidra single use containers will be disposed of.

Unused lenses will be returned to the manufacturer for credit where possible; and otherwise destroyed as per CORE SOP010_v02.

4.3.6 PRODUCT ACCOUNTABILITY

Accountability logs will be kept to include the number of lenses, lens care system bottles and single-use containers (or number of foil pouches containing 5 single-use containers) received, dispensed, unused and disposed of. All products dispensed to participants will be recorded in the study binder.

4.4 SCHEDULED AND UNSCHEDULED VISITS

This study has a total of 5 study visits, including the screening visit. Participants will attend CORE for a total of 4.75 hours. A summary of all study visits is shown in Table 1 below.

Table 1: Summary of visits

Visit code	Visits	Duration
1	Screening	**0.75 hrs**
2	Baseline & dispense (Day 0)	**1 hr**
3	Day 14 Follow-up (Day 14±2)	**1 hr**
4	Day 42 Follow-up (Day 42±4)	**1 hr**
5	Day 84 Follow-up (Day 84±6 & EXIT)	**1 hr**
Total		**4.75 hrs**

Potential participants who show an interest in the study will be provided with more details about the study over the phone as well as in writing (email script). A pre-screening questionnaire (Appendix 4) will be attached to the email script sent out to participants in the CORE database or to participants expressing an interest in the study, to determine the frequency and severity of their symptoms during a typical CL wear day. If interested, potential participants can return the questionnaires to CORE, in order to determine whether they may generally be suitable for the study based on the severity of their symptoms during CL wear. Participants meeting this criterion according to the categorization by Young et al[7] will be invited to a screening visit, where their full eligibility will be determined. Questionnaires completed prior to the consent procedure will not be included in the analysis. Volunteer participants may also be invited for a screening visit without previously completing the pre-screening questionnaire, however in order to save time and to avoid screen failures due to insufficient symptoms, completing the questionnaire prior to the screening visit is preferred.

4.4.1 SCREENING (VISIT 1)

Participants will attend the screening visit after having worn their current pair of habitual lenses (or new pair if daily disposable) for at least 6 hours prior to visit start. They will also be asked to bring their contact lens packaging as well as a bottle of cleaning solution (if applicable), to confirm habitual lens type parameters as well as solution. Study CL and solution will be ordered by CORE based on this information (or, if applicable, after over-refraction). The investigator will determine participant eligibility using the inclusion and exclusion criteria. Participants will be assigned a study ID number after they signed the informed consent document, and before their eligibility for the study has been confirmed. If all eligibility criteria have been met, a qualified investigator will be asked to review the eligibility criteria as well as medical history and medications to confirm that the Xiidra study drops can be dispensed to and used by a study participant. Only after the qualified investigator has confirmed eligibility and prescribed the drops, a participant will be invited for a baseline and dispense visit (V2). Ineligible participants will be discontinued from the study at the screening (or re-screen) visit.

The following evaluations/procedures will be performed:

- Informed consent;
- Participant demographics (age, sex);
- Contact lens history (current lens type; solution if applicable; wear days);
- CL wear time, comfortable wear time;
- Medical history and medications, including habitual rewetting drop use;
- Questionnaires
    - CLDEQ8;
    - Contact Lens Dry Eye Symptoms (categorization according to Young criterion)[7];
- Subjective ratings of ocular symptoms
    - Visual analog scales, including determination of Eye Dryness Score (EDS)[4,5] ;
- Monocular high contrast visual acuity (HCVA) with habitual CL, including over-refraction;
- Lens performance (fit & wettability) assessment (with habitual CL);
- Bulbar & limbal redness (with habitual CLs on eye; Efron scale & K5M);
- Lens removal;
- Slit lamp biomicroscopy using fluorescein (Safety)

4.4.2 BASELINE & DISPENSE (VISIT 2; DAY 0)

Participants will attend the baseline & dispense visit after having worn a **new** pair of their habitual lenses for at least 6 hours prior to visit start. No habitual eye drop use is permitted on the day of this study visit. Participants are asked to bring their habitual spectacles to the visit, to be worn prior to leaving the visit after Xiidra study drop application. Baseline measurements and evaluations will be performed prior to dispense of the Xiidra study drops.

The following evaluations/procedures will be performed, in the order outlined below:

- Changes in medical history and medications;
- Comfortable lens wear and total lens wear time;
- Questionnaires
    - CLDEQ8 questionnaire;
- Subjective ratings of ocular symptoms
    - Visual analog scales, including determination of Eye Dryness Score[4,5]
- Monocular high contrast visual acuity with habitual CL;
- Non-invasive tear break-up time over habitual CL (PLNITBUT);
- Lens performance (fit & wettability) assessment (with habitual CL);
- Bulbar & limbal redness (with habitual CLs on eye; Efron scale & K5M);
- Lens removal;
- Tear film collection;

- Slit lamp biomicroscopy using fluorescein (Safety);
- First application of Xiidra study drops
- Post-drop: Subjective ratings of symptoms and tolerability
- Monocular high contrast visual acuity with habitual spectacles or habitual CL;
- Dispense of Xiidra drops, including review of drop application process and frequency. Participants are also being reminded to not use the drops with CLs on eye;
- Dispense of habitual study lenses and care solution (if applicable) to last until the next study visit; one additional pair will be included to replace the new pair worn when attending this visit.

4.4.3 DAY 14 FOLLOW-UP (VISIT 3; DAY 14±2 DAYS)

Participants will attend the Day 14 Follow-Up visit after having worn a **new** pair of their habitual lenses for at least 6 hours prior to visit start. Participants may bring their habitual spectacles to the visit, to be worn after study measurements have been performed, or wear their habitual contact lenses when they leave at the end of the visit.

The following evaluations/procedures will be performed, in the order outlined below:

- Changes in medical history and medications;
- Comfortable lens wear and total lens wear time;
- Compliance (study drop use as well as CL wear frequency);
- Questionnaires
    - CLDEQ8 questionnaire;
- Subjective ratings of ocular symptoms
    - Visual analog scales, including determination of Eye Dryness Score[4,5]
- Monocular high contrast visual acuity with habitual CL;
- Non-invasive tear break-up time over habitual CL (PLNITBUT);
- Lens performance (fit & wettability) assessment (with habitual CL);
- Bulbar & limbal redness (with habitual CLs on eye; Efron scale & K5M)
- Lens removal;
- Tear film collection;
- Slit lamp biomicroscopy using fluorescein;
- Dispense of sufficient Xiidra drops to last until the next study visit;
- Dispense of sufficient habitual study lenses and care solution (as applicable) to last until the next study visit.

4.4.4 DAY 42 FOLLOW-UP (VISIT 4; DAY 42±4 DAYS)

Participants will attend the Day 42 Follow-Up visit after having worn a **new** pair of their habitual lenses for at least 6 hours prior to visit start. Participants may bring their habitual spectacles to the visit, to be worn after study measurements have been performed, or may wear their habitual contact lenses when they leave at the end of the visit.

The same study measurements as at V3 will be performed.

4.4.5 DAY 84 FOLLOW-UP (VISIT 5; DAY 84±6 DAYS)

Participants will attend the Day 84 Follow-Up visit after having worn a **new** pair of their habitual lenses for at least 6 hours prior to visit start. Participants may bring their habitual spectacles to the visit, to be worn after study measurements have been performed, or may wear their habitual contact lenses when they leave at the end of the visit.

The same study measurements as at V3 and V4 will be performed.

In addition, unused Xiidra study drops single use containers and unused contact lenses will be collected.

4.4.6 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.

4.4.7 STUDY EXIT

The Study Exit form must be completed when a participant exits the study. This will occur 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 been allocated a study ID number. Post-study follow-up visits will be scheduled if the investigator determines this is necessary and the exit form will be signed after the last follow-up visit.

At the Study Exit Visit the following details are required:

- Visual acuity with habitual lenses, spectacles or refraction (logMAR);
    - If the VA at the Exit Visit is two or more lines worse than at baseline, the investigator will be required to provide an explanation and complete an adverse event form.

- Post-study follow-up requirement (Y/N): If yes, the reason and date of the follow-up visit must also be recorded.

4.5 STUDY PROCEDURES

Table 2 summarizes the procedures at each visit. The order of procedures is described in sections 4.4.1 to 4.4.7.

Table 2: Summary of procedures to be conducted at scheduled visits

Procedure	Screening	Baseline/ Dispense	Day 14	Day 42	Day 84
Informed consent	X				
Participant demographics	X				
Contact lens history	X				
Comfortable & Total CL wear time	X	X	X	X	X
Medical history and medications	X				
Changes in medical history/medications		X	X	X	X
Compliance (Study drops & CL wear)			X	X	X
CLDEQ8	X	X	X	X	X
Symptoms via Young's criteria[6]	X				
Subjective Ratings (Visual Analog Scales)[4,5]	X	X	X	X	X
HCVA (logMAR)	X	X	X	X	X
PLNITBUT		X	X	X	X
Lens performance (fit & wettability)	X	X	X	X	X
Bulbar & limbal redness (Efron & K5M)	X	X	X	X	X
Lens removal	X	X	X	X	X
Tear collection		X	X	X	X
Biomicroscopy	X	X	X	X	X
Xiidra study drop application		X			
Study product dispense (drops & CL/solution)		X	X	X	X
Study product collection					X

4.5.1 CASE HISTORY

Demographics

At screening, the demographic information obtained from the participant will be age and sex.

Medical History

At screening, information will be obtained from participants about the current medication, allergies, and relevant medical conditions. At the Baseline & Dispense (V2) and Follow-up visits (V3 – V5), participants will be asked about changes in their medication or health.

Contact Lens History

Information will be obtained from the participant about the current contact lens type (lens name, brand), lens power, contact lens care solution, lens wear days, lens wear time (total and comfortable) and use of artificial tears.

4.5.2 QUESTIONNAIRES AND SUBJECTIVE RATINGS

Questionnaires

At screening; participants will be asked to assess the intensity and frequency of their CL associated dryness symptoms late in the day. Participant will be categorized as dry eye based on Young's categorization[7] (dark grey areas in Table 3 below):

Table 3: Young's categorization for contact lens dry eye score

Categorization grid for the Contact Lens Dry Eye score.

		Frequency of dryness				
		Never	Rarely	Sometimes	Frequently	Constantly
Intensity of late-day dryness	Never have it – 0	No	No	No	No	No
	Not at all intense – 1	No	No	No	No	No
	2	No	No	Marginal	Marginal	Marginal
	3	No	No	Yes	Yes	Yes
	4	No	No	Yes	Yes	Yes
	Very intense – 5	No	No	Yes	Yes	Yes

Note: Score derives from the combination of responses to frequency and intensity of dryness late in the day. Dark grey, Dry; light grey, Marginal; white, Not Dry.

Participants will complete the CLDEQ8 at every visit, reporting their experience with their habitual contact lenses in the last 2 weeks before a study visit.

Subjective ratings

Participants will be asked to complete subjective ratings of their ocular symptoms at each study visit. Participants will be asked to rate their ocular symptoms (OU) on a 7-item visual analog scale (VAS; Appendix 2) for a 0 (none) to 100 (worst) range; the VAS includes the following items: burning/stinging; itching; foreign body sensation; eye discomfort; eye dryness; photophobia; pain. At the screening visit, the eye dryness VAS rating needs to be >40 for a participant to be eligible.

4.5.3 VISUAL ACUITY

Visual acuity will be measured using high contrast computer-generated acuity charts. Participants will be asked to read letters that progressively decrease in size on a computer screen located at a distance of 6 meters. At the screening visit, additional trial lenses may be placed in front of the participant's eye to evaluate whether the participant's CL prescription needs to be optimized.

4.5.4 NON-INVASIVE BREAK-UP TIME (PRE-LENS)

The participant will be seated in front of a device that will project rings of light (Placido discs) onto the tear film. The participant will be asked to keep their eyes open for as long as they can and the time until the rings first begin to distort or break will be recorded. Three measurements will be taken to obtain an average value.

4.5.5 LENS PERFORMANCE

Contact lens fit

Lens fit will be assessed to ensure acceptable lens fit with a participant's habitual lenses at each of the visits.

Contact lens wettability

Contact lens wettability will be graded using 32x magnification, using a 0-4 scale, 0 = excellent wettability.

4.5.6 OCULAR REDNESS (WITH CL)

Ocular redness will be assessed for the bulbar and limbal conjunctiva, with CLs still on the eye. Assessments will include subjective grading using the EFRON Grading scale (0 to 4, 0 = normal; 0.1 increments) as well as objective measurements using the Keratograph K5M (0 to 4, 0.1 increments). To avoid potential investigator bias, subjective grades using the Efron scale will always be obtained prior to the K5M measurements.

4.5.7 TEAR FILM COLLECTION

Tears will be collected by holding a small, disposable, sterile glass tube near the participant's lower lid without touching the surface of the eye. During the procedure, participants will be allowed to blink normally. Tears will be collected from each eye until at least 5ul of basal tears have been collected, or after a maximum of 5 minutes collection time, whichever occurs first. All tear samples will be individually labeled with a study code (no participant names will be on these labels) and frozen until further processing. Tear samples will be analyzed for lipid and anti-inflammatory mediator concentration. Any remaining or resulting chemical combinations will be disposed of using standard laboratory procedures as outlined by the UW Safety Office.

4.5.8 SLIT LAMP BIOMICROSCOPY

The participant will be seated behind a slit lamp and the following will be assessed:

Cornea:

Any current or past corneal observations (such as infiltrates, old scars, etc) will be documented at each visit.

Corneal and conjunctival staining

A sodium fluorescein strip, wetted with a few drops of saline, will be applied to the superior bulbar conjunctiva of both eyes. Staining will be graded using the Efron scale (0 to 4, 0 = normal) while viewing with cobalt blue light through a Wratten no. 12 barrier filter.

Palpebral conjunctival hyperemia and roughness

The redness and roughness of the upper and lower eyelids (tarsal plate zone 2) will be assessed using the EFRON Grading scale (0 to 4, 0 = normal/ uniform satin appearance).

5 MONITORING PROTOCOL ADHERENCE

Guidelines to be included on adherence to visit windows and windows around other data collection points (i.e. subjective ratings). Procedures for monitoring and reporting deviations from the windows described in the protocol.

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, for at least 5 days/week and at least 6 hours/wear day. Adverse events and/ or complications in daily wear of soft contact lenses can occur (eg: inflammation and infection). 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. Participants will be wearing their habitual contact lens type in this study, there is no increased risk from wearing the lenses in this study. Due to the daily wear nature of the study, this study considered a non-significant risk study based on United States Food and Drug administration (FDA) and International Standards Organization (ISO) guidelines.

This study involves the use of lifitegrast ophthalmic solution 5% (Xiidra). Multiple previous studies have investigated the use of Xiidra in dry eye patients, with a typical exposure to the drops (2 applications/day) of up to 12 weeks or up to 6 months. In these studies, the most common ocular adverse reactions were eye irritation (18%), eye pain (13%) and instillation site reactions (12%); the majority of ocular adverse

reactions were mild and transient in nature. The most common non-ocular adverse reaction was dysgeusia (14%).

Participants may feel some eye irritation during and after the tear collection procedure. This irritation may be due to contact between the eyelid or lashes and the tip of the capillary tube or due to a temporary decrease in the volume of tears in their eye. In most cases, repeated blinking can alleviate this irritation in a very short period of time.

A dye (fluorescein) normally used for eye exams is being used in this study. Although rare, it is possible that participants may have any allergic reaction to the dye. This could cause discomfort to their eye.

Participants are advised to inform the investigator of any sensitivities to any ophthalmic drops or study products.

Participants may benefit directly from taking part in this study since they are receiving a recently introduced eye drop for treatment of dry eye that may also be used by CL wearers. Findings from this study will help researchers understand the effect of Xiidra when used by contact lens wearers, which might result in improved contact lens comfort. Participation in a study may contribute to scientific research information that may be used in the development of new contact lens products and eye drops.

7 ADVERSE EVENTS

See CORE SOP012_v02 for a description of all adverse events, including management and reporting.

An ‘adverse event’ (AE) refers to any untoward medical occurrence in a subject administered an investigational product or subjected to an investigational study procedure. Any observations taking place prior to determining that a subject meets all inclusion / exclusion criteria for the study and which are not related to the performed study procedures are not considered an AE. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporarily associated with the investigational product / study procedure, whether there is a causal relationship or not.

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

To maintain pharmaco-vigilance, information regarding all AEs, SAEs and pregnancies will be collected during the trial and reported according to local regulations. Clinical information about any adverse event will be collected on the standard CORE adverse events clinical report form. Serious adverse events will be reported within 24 hours to the Office of Research Ethics using their Adverse Event Report Form 106.

CORE will also inform the funding agency, Novartis, of all serious adverse events within 24 hours of becoming aware. Unusual failures in efficacy, reports of drug exposure during pregnancy and reports of study drug misuse or abuse, including initial and follow up reports, arising from the study in subjects exposed to the study drug will be reported to Novartis, as soon as it becomes available, but in any event within fifteen (15) calendar days of becoming aware of such information.

8 DISCONTINUATION FROM THE STUDY

Participants may be discontinued at the discretion of the investigator in consideration of participant safety or protocol compliance, or at discretion of the participant. Participants discontinued from a study will be reimbursed $20 per hour for their active involvement in the study (including the initial screening visit). Upon discontinuing, a participant will be offered the option of their data being withdrawn from future statistical analysis. 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 4.2.3.
- Unacceptable performance with products to be used in study: Participants may be discontinued if they are unable to achieve acceptable comfort and /or vision with the study products.
- Positive slit lamp finding: Participants may be 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 CORE or the Office of Research Ethics at the University of Waterloo.

A discontinuation form (ADMIN 3), stating the reason for discontinuation, 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.

All discontinuations including their reasons will be included in the final report.

9 STUDY COMPLETION AND REMUNERATION

At the last scheduled protocol visit a study completion form (ADMIN 2) 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 (ADMIN 1).

Once their involvement in the study is complete, participants will be informed about receiving feedback following study completion in the Letter of Appreciation (ADMIN 1).

Participant remuneration will be $95 for completing the study. Participants will be asked to sign a Study remuneration form (ADMIN 4), acknowledging that they have received remuneration for their involvement in the study.

10 STATISTICAL ANALYSIS AND DATA MANAGEMENT

10.1 STATISTICAL ANALYSIS

All data will be analyzed by CORE at the University of Waterloo. Unmasked data analysis will be conducted using Statistica 13 or later. Descriptive statistics will be provided on information regarding baseline variables (age, sex, refractive error distribution, etc.). For data collected on each eye individually (e.g. biomicroscopy), results of the right eye will be reported unless a difference between right eye and left eye is found. Table 3 lists the primary and other outcome variables and anticipated statistical procedures. All data will be tested for normality of distribution using Shapiro-Wilk tests. Statistical significance will be set at 5%. Superiority testing for the primary outcome variable (i.e. VAS ratings for CL-related discomfort and dryness at 12–weeks vs baseline) will be performed, using a superiority margin of 10 units on the 100-point scale. Additional statistical testing may be applied as required.

Table 4: Statistical procedures

Variable	Analysis	Statistical test
• CLDEQ-8 score, • VAS ratings, • Pre-lens non-invasive tear break-up time (PLNITBUT), • bulbar and limbal redness, • tear inflammatory markers;	Descriptive statistics	Mean, Standard Deviation
	Effect of time on the outcome variables *(Comparison between visits)*	RMANOVA/MANOVA Mauchly's test of sphericity Huynh-Feldt p values Tukey HSD post hocs Paired t-test
Safety measures (biomicroscopy, visual acuity.)	Descriptive statistics	Mean, Standard Deviation
	Effect of safety and exploratory variables over time	RMANOVA/MANOVA Mauchly's test of sphericity Huynh-Feldt p values Tukey HSD post hocs Paired t-test

10.2 DATA MANAGEMENT

Data from this study will be retained by CORE for a minimum of 25 years on a password-protected server. After 25 years, data will be disposed of in accordance with the guidelines laid out by the University of Waterloo.

At the completion of the study CORE may provide a copy of the study data to the funding agency, Novartis, when requested. Data will typically be sent using a secure file share system operated by the University of Waterloo called Sendit which uses 128bit (or 256bit) SSL encryption. This system provides a secure way to transfer files when email is not appropriate, whether because of file size, file type or concerns over security. Sendit includes features such as password protection, a restricted time period for download, IP logging and email notification of download. Files may be encrypted prior to transmission upon request. Using this method means that data files are only stored on University of Waterloo servers during the transfer.

10.3 COMMENTS ON SOURCE DOCUMENTS

Data analysis will not be conducted on comments which have been recorded in the source documents. Only highlighted 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.

11 PROTOCOL TRAINING

All study personnel will be required to complete training prior to their involvement in the study. A series of training modules will be developed for the study and records of training will be kept at CORE.

12 STUDY MONITORING

Status reports will be provided to the funding agency, Novartis 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 will be conducted by CORE personnel. Consent documentation will be reviewed by a person not involved in the consent process. To monitor data integrity, data entry will be conducted by two people and the entries will be compared. All adverse events and protocol deviations will be reviewed by the Lead Investigator. All serious adverse events and major protocol deviations will be reviewed by the Qualified Investigator and the Principle Investigator.

13 STUDY MANAGEMENT

13.1 STATEMENT OF COMPLIANCE

This clinical study is designed to be in compliance with the ethical principles in the Declaration of Helsinki, with the ICH guidelines for Good Clinical Practice (GCP), with the University of Waterloo's Guidelines for Research with Human Participants and with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2nd Edition.

- Declaration of Helsinki
- ICH E6 - International Conference on Harmonisation; Good Clinical Practice
- http://iris.uwaterloo.ca/ethics/human/guidelines/index.htm
- http://iris.uwaterloo.ca/ethics/human/ethicsReview/UWStatement.htm
- http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/

13.2 ETHICS REVIEW

This protocol will be submitted to and reviewed through the Office of Research Ethics (ORE) at the University of Waterloo. Notification of ethics clearance of the application is required prior to the commencement of the study.

13.3 CLINICAL TRIAL REGISTRATION

CORE will register this study with clinicaltrials.gov.

13.4 PROTOCOL DEVIATIONS

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

13.4.1 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 ORE:

- Changes in procedures initiated to eliminate immediate risks/hazards to participants;
- Enrollment of participants outside the protocol inclusion/exclusion criteria;
- Medication / device / intervention errors (i.e. incorrect drug or dosage of drug / incorrect contact lens(es) dispensed / incorrect care system dispensed);
- 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.

13.4.2 MINOR PROTOCOL DEVIATIONS

Protocol deviations caused by or which originate with research participants are considered minor, and normally are not reported to the ORE unless these result in increased risk to the participant(s). 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).

13.4.3 REPORTING AND DOCUMENTING PROTCOL DEVIATIONS

Major protocol deviations must be reported to the ORE within 7 days of the deviation occurring (or its discovery) 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.

13.5 PREMATURE TERMINATION OF THE STUDY

CORE or the Office of Research Ethics at the University of Waterloo may terminate the study at any time for any reason.

13.6 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 study exit.

13.7 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 CORE SOP014_v01_Clinical data management.

14 REPORT

A report will be sent to the funding agency, Novartis, according to terms described in the study contract.

15 REFERENCES

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2. Begley CG, Chalmers RL, Mitchell GL, Nichols KK, Caffery B, Simpson T, DuToit R, Portello J, Davis L. Characterization of ocular surface symptoms from optometric practices in North America. Cornea 2001;20:610-8.
3. Schultz CL, Kunert KS. Interleukin-6 levels in tears of contact lens wearers. J Interferon Cytokine Res 2000;20:309-10.
4. Holland EJ, Luchs J, Karpecki PM, Nichols KK, Jackson MA, Sall K, Tauber J, Roy M, Raychaudhuri A, Shojaei A. Lifitegrast for the Treatment of Dry Eye Disease: Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3). Ophthalmology 2017;124:53-60.
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7. Young G, Chalmers R, Napier L, Kern J, Hunt C, Dumbleton K. Soft Contact Lens-Related Dryness with and without Clinical Signs. Optometry Vision Sci 2012;89:1125-32..
8. Xiidra (Lifitegrast Ophtalmic Solution 5% w/v) product monograph