Alcon

Device Protocol for CLV201-C002 / NCT05211739
Title: Clinical Assessment of a Daily Wear Monthly Replacement Silicone Hydrogel Toric Contact Lens

Protocol Number:	CLV201-C002
Clinical Investigation Type:	Pivotal
Test Product:	[redacted] Toric soft contact lenses
Sponsor Name and Address:	Alcon Research, LLC, and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices; applicable international and national regulations, laws, guidelines, and standards; the conditions of approval imposed by the reviewing IRB or regulatory authority; and in accordance with the ethical medical research principles outlined in the Declaration of Helsinki.
- I will supervise all testing of the device involving human subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental regulations.
- I have read and understand the appropriate use of the investigational product(s) as described in the protocol, current investigator's brochure, product information, or other sources provided by the sponsor.
- I understand the potential risks and side effects of the investigational product(s).
- I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements of the sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal investigator:

Signature Date

Name and professional position:

Address:

Phone Number:

Off-hours Emergency Phone Number:

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[redacted]

1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as [redacted] Toric soft contact lenses or [redacted] Toric contact lenses (LID205255).
Name of Comparator Product(s)	CooperVision® Biofinity® Toric (comfilcon A) contact lenses will be referred to as Biofinity Toric.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (investigational product) or comparator product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational medical device (investigational product) or comparator product.*
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (investigational product). *Note: This definition includes events related to the investigational medical device, comparator, or the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices (investigational product) or comparator product.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect	An effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

(ASADE)	
Clinical Investigation Plan (CIP)	The document(s) stating the rationale, objectives, design, and prespecified analysis, methodology, organization, monitoring, conduct, and record-keeping of the clinical investigation. *Note: The protocol and other documents referenced in the protocol (for example, the Statistical Analysis Plan, the Manual of Procedures, the Deviations and Evaluability Plan, and the Protocol Monitoring Plan) comprise the CIP.*
Clinical Investigation Report (CIR) / Clinical Study Report	The document describing the design, execution, statistical analysis, and results of a clinical investigation. The Clinical Investigation Report is synonymous with the Clinical Study Report.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.* Requirements for reporting Device Deficiencies in the study can be found in Section 11.
Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Point of Enrollment	The time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form.
Interventional Clinical Trial	A pre- or postmarket clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a clinical investigation plan, or diagnostic or monitoring procedures requested in the CIP are

	in addition to those available as normal clinical practice and burden the subject.
Investigational Product	A preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or comparator product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (CIP), or investigator's brochure (IB).
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Randomized Subject	Any subject who is assigned a randomized treatment.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a) a life-threatening illness or injury *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.*

	b) any potentially sight-threatening event or permanent impairment to a body structure or a body function including chronic diseases. c) inpatient hospitalization or prolonged hospitalization. d) a medical or surgical intervention to prevent a) or b). e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, congenital abnormality or birth defect including physical or mental impairment. *Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* *Refer to Section 11 for additional SAEs.*
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons. *Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Significant Nonserious Adverse Event	A symptomatic, device-related, non-sight-threatening adverse event that warrants discontinuation of any contact lens wear for greater than or equal to 2 weeks. *Refer to Section 11 for additional Significant Nonserious AEs.*

Study Start	The start of the study is considered to coincide with the enrollment of the first patient.
Study Completion	The completion of the study is considered to coincide with the study-level last subject last visit or the decision to terminate the trial, whichever is later.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk assessment.
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. *Note:* *a) Use error includes the inability of the user to complete a task.* *b) Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.* *c) Users might be aware or unaware that a use error has occurred.* *d) An unexpected physiological response of the patient is not by itself considered a use error.* e) *A malfunction of a medical device that causes an unexpected result is not considered a use error."*
Vulnerable Subject	An individual who is unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

2 LIST OF ACRONYMS AND ABBREVIATIONS

Table 2–1 List of Acronyms and Abbreviations Used in This Protocol

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
BCVA	Best corrected visual acuity
Biofinity Toric	CooperVision® Biofinity® Toric (comfilcon A) contact lenses
CFR	Code of Federal Regulations
CI	Confidence interval
CIP	Clinical investigation plan
CIR	Clinical investigation report
COL	Clinical operations lead
CRF	Case report form
CSM	Clinical study manager
CTT	Clinical trial team
[redacted]	[redacted]
D/C	Discontinue
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GPCMS	Global Product Complaint Management System
[redacted]	[redacted]
IB	Investigator's brochure
ICF	Informed consent form
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
LID	Lens Identification Number
LogMAR	Logarithm of the minimum angle of resolution
[redacted]	[redacted]
MOP	Manual of procedures
N	Number of subjects
N/A	Not applicable
OD	Right eye
OS	Left eye
[redacted] Toric	[redacted] Toric contact lenses (LID205255)
PP	Per protocol
SADE	Serious adverse device effect
SAE	Serious adverse event

Abbreviation	Definition
SD	Standard deviation
SLE	Slit lamp examination
SOP	Standard operating procedure
US or USA	United States
USADE	Unanticipated serious adverse device effect
VA	Visual acuity
[redacted]	[redacted]

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Pivotal
Investigational products	Test Product: [redacted] Toric (LID205255) Comparator Product: Biofinity Toric
Purpose and Scientific Rationale for the Study	The overall objective of this clinical study is to describe the clinical performance of the investigational [redacted] Toric contact lenses over 30 days of daily wear.
Objective(s)	The primary objective is to evaluate visual acuity of the [redacted] Toric soft contact lenses. [redacted]
Endpoint(s)	Primary Effectiveness • Distance VA (logMAR) with study lenses [redacted]

	[redacted]
	Safety • Adverse events • Biomicroscopy findings • Device deficiencies
Assessment(s)	Effectiveness • Distance VA (logMAR)
	[redacted]
	• Distance VA (logMAR) with habitual lenses • Manifest refraction

	• BCVA (Snellen distance with manifest refraction) • Keratometry Safety • Adverse Events • Biomicroscopy • Device deficiencies
Study Design	This is a prospective, randomized, bilateral, crossover, double-masked study comparing the [redacted] Toric and Biofinity Toric contact lenses. Subjects will be randomized 1:1 to receive one of two sequences: Sequence 1 = LID205255/Biofinity Toric Sequence 2 = Biofinity Toric/LID205255 Subjects will be exposed to both lenses for a total of approximately 60 days (approximately 30 days for each lens).
Subject population	Planned number of subjects enrolled/consented: ~72 Planned number of completed subjects: 58 The study population consists of volunteer subjects aged 18 or over who are habitual toric weekly/monthly soft contact lens wearers, have at least 3 months of contact lens wearing experience, and who wear their habitual lenses at least 5 days per week and at least 10 hours per day.
Sites and Locations	Planned number of clinical sites: ~ 6 Planned locations (initial list of locations, which may change during start up or conduct according to study needs): United States
Key inclusion criteria (See Section 8.1 for a	• Successful wearer of weekly/monthly toric soft contact lenses in both eyes for a minimum of 5 days per week and 10 hours per day during the past 3 months.

complete list of inclusion criteria)	• Best corrected distance visual acuity (as determined by manifest refraction at screening) better than or equal to 20/25 in each eye.
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Monovision and multifocal contact lens wearers. • Daily disposable contact lens wearers. • Habitual Biofinity Toric/Biofinity Toric XR contact lens wearers in the past 3 months prior to consent.
Data analysis and sample size justification	**Planned Data Analysis** To address the primary [redacted] only descriptive statistics will be provided. No inferential testing will be performed. **Sample Size Justification** Degree of precision achieved [redacted] a sample size of 58 is as follows: Visual Acuity: with an assumed standard deviation (SD) of 0.05, a two-sided 95% confidence interval (CI) for the mean difference, with coverage probability of 0.90, will extend 0.02 from the observed mean. [redacted]
Associated materials	• CLEAR CARE® contact lens solution • Lubrication/rewetting drops will not be permitted during lens wear. However, habitual lubrication/rewetting drop usage is allowed up to 10 minutes prior to lens insertion and any time after lens removal. • No lubrication/rewetting drop use will be allowed during clinic visits. • LacriPure saline will be permitted for rinsing the lens(es) if needed.

Table 3–1 Schedule of Study Procedures and Assessments

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screen / Baseline [redacted]	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 4 Dispense Lens 2**	**Visit 5 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled visit**	**Early Exit**
Procedure/ Assessment		**Day 1** [redacted]	**Day 30 (-1/+3) Days**	**Day 1** [redacted]	**Day 30 (-1/+3) Days**	**N/A**	**N/A**
Informed Consent	X						
Demographics	X						
Medical History∞	X	X	X	X	X	X	X
Concomitant Medications∞	X	X	X	X	X	X	X
Inclusion/Exclusion	X						
Habitual lens information (brand, power*, lens care)	X						
VA with habitual correction (OD, OS, Snellen distance)*	X				X	(X)	X
Keratometry (OD, OS)	X						
Manifest refraction*	X	(X)	(X)	(X)	(X)	(X)	(X)
BCVA* (OD, OS, Snellen distance with manifest refraction)	X	(X)	(X)	(X)	(X)	(X)	(X)
Biomicroscopy	X	X	X	X	X	X	X

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screen / Baselin	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 4 Dispense Lens 2**	**Visit 5 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled visit**	**Early Exit**
Procedure/ Assessment		**Day 1**	**Day 30 (-1/+3) Days**	**Day 1**	**Day 30 (-1/+3) Days**	**N/A**	**N/A**
						Optional with ULR only	
Randomization	X						
Determine study lens power parameters*	X						
Dispense study lenses*		X		X		(X)	

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screen / Baselin	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 4 Dispense Lens 2**	**Visit 5 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled visit**	**Early Exit**
Procedure/ Assessment		**Day 1**	**Day 30 (-1/+3) Days**	**Day**	**Day 30 (-1/+3) Days**	**N/A**	**N/A**
[redacted]							
VA w/study lenses (OD, OS, logMAR distance)		X	X	X	X	X	X
[redacted]							

		LENS 1 (Period 1)		LENS 2 (Period 2)			
	Visit 1 Screen / Baseline [redacted]	**Visit 2 Dispense Lens 1**	**Visit 3 Day 30 Follow-up Lens 1**	**Visit 4 Dispense Lens 2**	**Visit 5 Day 30 Follow-up Lens 2 / Exit**	**Unscheduled visit**	**Early Exit**
Procedure/ Assessment		**Day 1** [redacted]	**Day 30 (-1/+3) Days**	**Day 1** [redacted]	**Day 30 (-1/+3) Days**	**N/A**	**N/A**
[redacted]							
Adverse Events	X	X	X	X	X	X	X
Device deficiencies	X	X	X	X	X	X	X
Exit Form	(X)	(X)	(X)	(X)	X		X

[redacted]

4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the study sponsor and must be approved by the IRB/IEC and global and regional Health Authorities, as applicable, prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.

Refer to Appendix A for detailed description of amendments.

5 INTRODUCTION

5.1 Rationale and Background

[redacted] Toric soft contact lenses are a new monthly replacement water gradient contact lens with a gradual transition from a 55% water, highly breathable core, to a surface that is nearly 100% water. The toric lens utilizes the Precision Balance 8|4™ ballasted toric design.

Lehfilcon A toric soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic (having the natural eye lens) or aphakic (not having the natural eye lens) persons with nondiseased eyes with up to 6.00 diopters (D) of astigmatism.

The lenses are intended for daily wear (less than 24 hours while awake) with removal for cleaning and disinfection (chemical, not heat) prior to reinsertion, or disposal. Lenses should be discarded after one month.

[redacted] These new silicone hydrogel lenses have been designed to provide favorable performance for daily wear with 1-month replacement.

In this clinical study, the clinical performance of the investigational [redacted] Toric contact lens will be assessed and the [redacted] Toric contact lens will be compared to the commercially available Biofinity Toric contact lens in a crossover dispense trial, both to be worn in a daily wear modality and replaced on a monthly basis.

5.2 Purpose of the Study

The purpose of this study is to assess the clinical performance of the investigational [redacted] Toric contact lens over 30 days of daily wear. The primary endpoint was selected to address the primary objective of the study. Procedures for measurement of these endpoints were selected based on common practice for these assessments. The design of this study is justified based upon preclinical and clinical testing, as described within the Investigator's Brochure. Biofinity Toric contact lenses were chosen as the comparator product because these lenses have the same wear modality and replacement schedule.

At the end of the study, a clinical study report will be prepared in accordance with applicable regulatory requirements and standards.

[redacted]

5.3 Risks and Benefits

The clinical investigation process risks are managed through appropriate training and monitoring according to the protocol-specific monitoring plan. Investigational device risks, including risks associated with use of device and methods and procedures for application of device, are defined in the investigator's brochure and/or product labeling and are managed through review of safety assessments outlined in this protocol.

There may also be unknown risks to use of [redacted] Toric. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight and monitoring.

Refer to the product label for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
Evaluate visual acuity of the [redacted] Toric soft contact lenses.	Distance VA (logMAR) with study lenses

6.2 Secondary Objective(s)

Not applicable.

[redacted]

6.4 Safety Objective(s)

Table 6–3 Safety Objective(s)

Objective(s)	Endpoint(s)
Describe the safety profile of the study products	• Adverse events • Biomicroscopy findings • Device deficiencies

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, randomized, bilateral, crossover, double-masked, trial comparing the [redacted] Toric and Biofinity Toric contact lenses.

Subjects will be randomized in 1 of 2 crossover sequences and exposed to both test and comparator lenses for bilateral wear. Subjects will be expected to attend 5 office visits and will be dispensed study lenses (test and comparator lenses) for 30 day duration of bilateral wear with each study lens (~60 days of lens wear). Subject will wear the study lenses for 10-12 hours on the Day 1, [redacted] and prior to the Day 30 visit [redacted] Subjects will be expected to wear their study contact lens at least 5 days per week, over a 30 day period per study lens.

In this trial, both investigator and subject will be masked and an unmasked site coordinator will prepare the lenses for dispensing.

All study contact lenses will be prescribed according to subject's prescription. CLEAR CARE contact lens solution will be used during the duration of the study.

[redacted]

7.2 Rationale for Study Design

This study design is justified based upon an evaluation of the results of relevant preclinical and clinical testing, as described within the IB.

The bilateral, crossover study design will ensure that the same subject is exposed to both the test and comparator lens materials during the study visits and wearing period; therefore, [redacted] assessments can be obtained for both lenses from the same subject. The study will include only those subjects who are successful wearers of soft toric contact lenses in both eyes during the past 3 months for a minimum of 5 days per week and 10 hours per day. This will avoid confounding safety responses in nonadapted subjects. Moreover, the subjects will not be permitted to use artificial tears/rewetting drops during study participation as this may confound the primary effectiveness [redacted] The study will exclude any habitual Biofinity Toric/Biofinity Toric XR contact lens wearers in the past 3 months prior to consent in order to reduce potential bias of wearers to their habitual contact lenses. The study will also exclude subjects who are monovision or multifocal contact lens wearers and daily disposable contact lens wearers.

7.3 Rationale for Duration of Treatment/Follow-Up

The primary [redacted] endpoint will be assessed on Day 1 and Day 30. Hence, subjects will wear each study product bilaterally for approximately 30 days.

7.4 Rationale for Choice of Comparator Product

Biofinity Toric contact lenses were chosen as the comparator product as these lenses have the same wear modality and replacement schedule as [redacted] Toric contact lenses.

7.5 Data Monitoring Committee

Not applicable

8 STUDY POPULATION

The study population consists of volunteer subjects aged 18 or over who are habitual toric weekly/monthly soft contact lens wearers, have at least 3 months of contact lens wearing experience, and who wear their habitual lenses at least 5 days per week and at least 10 hours per day. It is aimed to enroll (consent) approximately 72 subjects at approximately 6 sites in the United States, with a target of 58 total subjects completed. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 8 weeks; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol.

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Subjects must be at least 18 years of age
2. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form.
3. Subject must be willing and able to attend all study visits as required per protocol.
4. Successful wearer of weekly/monthly toric soft contact lenses in both eyes for a minimum of 5 days per week and 10 hours per day during the past 3 months.
5. Best corrected distance visual acuity (as determined by manifest refraction at screening) better than or equal to 20/25 in each eye.
6. Able to wear contact lenses within a range of sphere & cylinder power and axes [redacted]
7. Subject must be willing to stop wearing their habitual contact lenses for the duration of the study participation.
8. Subject must possess spectacles and willing to wear habitual spectacles for vision correction when study lenses are not worn, as needed,[redacted]

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study.

1. Any anterior segment infection, inflammation, or abnormality or disease (including systemic) that contraindicates contact lens wear, as determined by the investigator

2. Any use of systemic or ocular medications for which contact lens wear could be contraindicated, as determined by the investigator.

3. History of refractive surgery or plan to have refractive surgery during the study or irregular cornea in either eye.

4. Ocular or intraocular surgery (excluding placement of punctal plugs) within the previous 12 months or planned during the study.

5. Biomicroscopy findings at screening that are moderate (Grade 3) or higher and/or corneal vascularization that is mild (Grade 2) or higher; presence of corneal infiltrates

6. Current or history of pathologically dry eye in either eye that, in the opinion of the -nvestigator, would preclude contact lens wear.

7. Current or history of herpetic keratitis in either eye.

8. Eye injury in either eye within 12 weeks immediately prior to enrollment for this trial.

9. Current or history of intolerance, hypersensitivity or allergy to any component of the study products.

10. Any use of topical ocular medications and artificial tear or rewetting drops that would require instillation during contact lens wear.

11. The investigator, his/her staff, family members of the investigator, family members of the investigator's staff, or individuals living in the households of the aforementioned persons may not participate in the study.

12. Participation of the subject in a clinical trial within the previous 30 days or currently enrolled in any clinical trial.

13. Monovision and multifocal contact lens wearers.

14. Daily Disposable contact lens wearers

15. Habitual Biofinity Toric/Biofinity Toric XR contact lens wearers in the past 3 months prior to consent.

16. Wearing habitual contact lenses in an extended wear modality (routinely sleeping in lenses for at least 1 night per week) over the last 3 months prior to enrollment.

8.3 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): [redacted] Toric

Comparator Product(s) (If applicable): Biofinity Toric

Table 9–1 Test Product

Test Product	[redacted] Toric
Lens Identification Number (LID)	LID205255
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	The intended use of this product is for vision correction.
Product description [redacted]	• Material: Lehfilcon A • Water content: 55% • Base curve (mm): 8.6 (Target) • Diameter (mm): 14.5 (Target) [redacted]

	[redacted]
Formulation	Refer to IB

Usage	• Wear:
	  ○ Daily Wear
	  ○ Bilateral
	• Replacement period: 30-day replacement
	• Exposure: 10-12 hours on the Day 1, [redacted] and prior to the Day 30 visit [redacted]
	• Replacement period: Replacement lenses will not be provided to the subject. In the event a lens needs to be replaced, the subject must return to the site for a replacement lens. Until the replacement lens is obtained, the subject must store the fellow lens in the provided lens care solution and wear their habitual spectacles.
	• Lens Care: Cleaned and disinfected with the assigned lens care after each use

Number/Amount of product to be provided to the subject	Subjects will insert study lenses at Visit 2 and Visit 4 at the site. No spare lenses will be provided to the subject.
Packaging description	Blister foil pack

Labeling description	• Lens Foil label includes at a minimum:
	  - Identifier
	  - base curve
	  - diameter
	  - manufacturing protocol number
	  - packing solution
	  - power

	- lot number - expiration date - content statement - investigational device statement - sponsor information - Country of origin • Provided in ~24 lenses per power per package, identified with the following at a minimum: - a color coded label stating the protocol number - LID number - power - an investigational use only statement - Handling unit number
Training and/or experience requirements for device	No additional training or experience is required to administer the test product.
Storage conditions	Lenses are to be stored at room temperature
Supply	• Lenses supplied by the Sponsor • CLEAR CARE contact lens solution supplied by Sponsor to be provided to the subject • LacriPure saline will be permitted for rinsing the lens(es) if needed.

Table 9–2 Comparator Product

Comparator Product(s)	CooperVision® Biofinity® Toric (comfilcon A) contact lenses *No Biofinity Toric XR*
Manufacturer	CooperVision
Indication for Use	The intended use of this product is for vision correction.
Product description [redacted]	• Material: comfilcon A • Water content: 48% • Base curve (mm): 8.7

[redacted]	• Diameter (mm): 14.5 [redacted]
Formulation	Refer to package insert
Usage	• Wear: ○ Daily Wear ○ Bilateral • Replacement period: 30-day replacement • Exposure: 10-12 hours on the Day 1, [redacted] and prior to the Day 30 visit [redacted] • Replacement period: Replacement lenses will not be provided to the subject. In the event a lens needs to be replaced, the subject must return to the site for a replacement lens. Until the replacement lens is obtained, the subject must store the fellow lens in the provided lens care solution and wear their habitual spectacles. • Lens Care: Cleaned and disinfected with the assigned lens care after each use
Number/Amount of Product to be Provided to the subject	Each site will procure their own comparator lenses.
Packaging description	Provided in commercial packaging
Labeling description	Commercial foil
Training and/or experience	No additional training or experience is required to administer the comparator product.

requirements for device	
Storage conditions	Lenses are to be stored at room temperature
Supply	• Each site will procure their own comparator lenses. • CLEAR CARE contact lens solution supplied by Sponsor to be provided to the subject • LacriPure saline will be permitted for rinsing the lens(es) if needed.

More information on the test product can be found in the [redacted] investigator's brochure; information on the comparator product can be found in the Biofinity Package Insert.

9.2 Other Medical Device or Medication Specified for Use During the Study

No other medical devices or medications are required to be used in conjunction with the treatments during the clinical study.

9.3 Treatment Assignment / Randomization

Subjects will be randomized in a 1:1 ratio to receive treatment (lens) in crossover sequence of Test product then Comparator product or Comparator product then Test product, respectively.

Sequence	**EDC/randomization integration system**	**Lens Name**
Sequence 1	LID205255/Biofinity Toric	[redacted] Toric/Biofinity Toric
Sequence 2	Biofinity Toric/ LID205255	Biofinity Toric/[redacted] Toric

Only after signing the ICF, a subject will be assigned a subject number by the electronic data capture system.

A randomization list will be generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned treatment according to the randomization list uploaded in the randomization system. The randomization list will be generated and maintained by the study sponsor.

At Visit 1, all eligible subjects will be randomized via the EDC/randomization integration to one of the treatment arms. The investigator's delegate will access the respective system after

confirming that the subject meets all the eligibility criteria. A randomization number will be automatically assigned to the subject according to the subject randomization list but will not be communicated to the site user. The EDC/randomization integration system will inform the site user of the treatment sequence (lens sequence) assignment to be dispensed to the subject.

9.4 Treatment masking

This study is double-masked, with subjects randomized in a 1:1 ratio to receive [redacted] Toric and Biofinity Toric contact lenses in a crossover sequence for the duration of the two 30-day treatment period. [redacted]

[redacted]

[redacted] Unmasking will occur only after all planned study data have been validated, and the database locked.

Masked study personnel must avoid seeking information that may compromise masking. [redacted]

In the event of a medical emergency where the knowledge of subject treatment is required, an individual investigator will have the ability to unmask the treatment assignment for a specific subject after contacting an appropriate study sponsor representative if time allows.

9.5 Accountability Procedures

Upon receipt of the IPs, the investigator or delegate must conduct an inventory. [redacted] Throughout the study, the investigator or delegate must maintain records of IP dispensation and collection for each subject. This record

must be made available to the study monitor for the purposes of verifying the accounting of IP supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. All IPs sent to the investigator must be accounted for by study sponsor personnel, and in no case be used in an unauthorized situation.

The investigator should make every effort to collect unused lenses, foils, and supplies from subjects.

It is the investigator's responsibility to ensure that:

- All study products are accounted for and not used in any unauthorized manner
- All unused products are available for return to the study sponsor, as directed
- Any study lenses associated with a device deficiency or with any product-related adverse event (i.e., ADE or SADE) are returned to the study sponsor for investigation, unless otherwise directed by the sponsor. Refer to Section 11 of this protocol for additional information on the reporting of device deficiencies and AEs and the return of study products associated with these events.

The investigator is responsible for proper disposition of all unused IPs at the conclusion of the study, according to the instructions provided in the MOP.

9.6 Changes to concomitant medications, treatments/ procedures

After the subject is enrolled into the study, the investigator must instruct the subject to notify the study site about:

- Any new medications
- Alterations in dose or dose schedules for current medications,
- Any medical procedure or hospitalization that occurred or is planned
- Any nondrug therapies (including physical therapy and blood transfusions).

The investigator must document this information in the subject's case history source documents.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 Informed Consent and Screening

The investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document.

The investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

10.2 Description of Study Procedures and Assessments

Detailed descriptions of assessments and procedures are provided in the MOP. The investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

10.2.1 Demographics

Obtain demographic information including age, race, ethnicity, and sex.

10.2.2 Medical History

Collect medical history information, including information on all medications used within the past 30 days. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications. Throughout the subject's participation, obtain information on any changes in medical health and/or the use of concomitant medications.

Medical History and Concomitant Medications will be collected in the eCRF as outlined in the MOP.

10.2.3 Investigational Product compliance

Review subject compliance with the IP usage and adjunct product usage and collect all used and unused study IPs and other products that were dispensed.

10.2.4 Adverse Event Collection: Safety Assessment

Assess and record any adverse events that are observed or reported since the previous visit, including those associated with changes in concomitant medication dosing.

10.2.5 Slit Lamp Biomicroscopy: Safety Assessment

SLE of the cornea, iris/anterior chamber and lens must be performed in both eyes before instillation of any diagnostic eye drops.

10.2.6 Device Deficiencies: Safety Assessment

Assess and record any Device Deficiencies that are reported or observed since the previous visit. Requirements for reporting device deficiencies in the study can be found in Section 11.

10.3 Unscheduled Visits

If a subject visit occurs between any regularly scheduled visit and the visit is conducted by study personnel, this visit must be documented as an Unscheduled Visit. If the subject seeks medical attention outside the clinic (for example, at an Emergency Room) or at the clinic but is seen by nonstudy personnel, the investigator is to capture adverse event-related information on the Adverse Event form upon becoming aware.

During all unscheduled visits, the investigator must conduct the following procedures:

- Collect Adverse Event information
- Collect device deficiency information
- Record changes in medical condition or concomitant medication
- Perform a biomicroscopy
- VA w/study lenses (OD, OS, logMAR distance)

The investigator may perform additional procedures for proper diagnosis and treatment of the subject. The investigator must document this information in the subject's case history source documents.

If during an Unscheduled Visit the subject is discontinuing the IP or discontinuing from the study, the investigator must conduct Exit procedures according to Table 3–1 Schedule of Study Procedures and Assessments and Section 10.4.3, as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to, randomization to product/dispense of study product.

The investigator must document the reason for screen failure in the subject's case history source documents.

Subject numbers must not be reused.

10.4.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the investigator after signing informed consent.

Subject numbers of discontinued subjects must not be re-used (i.e., subject replacement is not allowed).

Subjects may discontinue from study or study treatment at any time for any reason. Subjects may also be discontinued from study treatment at any time if, in the opinion of the investigator, continued treatment poses a risk to their health.

If a subject discontinues from study treatment, every effort must be made to keep the subject in the study and to continue with the study assessments as specified in the schedule of study procedures and assessments until the final visit.

For subjects discontinuing from the study, the investigator must complete all Exit procedures according to Table 3–1 Schedule of Study Procedures and Assessments and Section 10.4.3, if the subject is willing and able, and if in the opinion of the investigator it is safe for the subject to do so.

The investigator must document the reason for study or treatment discontinuation in the subject's case history source documents.

To ensure the safety of all subjects who discontinue early, investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

10.4.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product

Other than screen failures, if a subject discontinues from the study, the subject should undergo an Early Exit Visit. Refer to Table 3–1.

10.5 Clinical Study Termination

The study sponsor reserves the right to suspend or close the investigational site or suspend or terminate the study in its entirety at any time.

If the clinical study is prematurely terminated or suspended by the study sponsor:

- The study sponsor must:
    - Immediately notify the investigator(s) and subsequently provide instructions for study termination.
    - Inform the investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The investigator must:
    - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.
    - Provide subjects with recommendations for post-study treatment options as needed.

The investigator may terminate the site's participation in the study for reasonable cause.

Breaking of the masked treatment codes will be done after locking the database.

10.5.1 Follow-up of subjects after study participation has ended

Following this study, the subject will return to their eye care professional for their routine eye care.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons,

whether or not related to the investigational medical device (test product). Refer to the Glossary of Terms and figures below for categories of AEs and SAEs.

Figure 11–1 Categorization of All Adverse Events

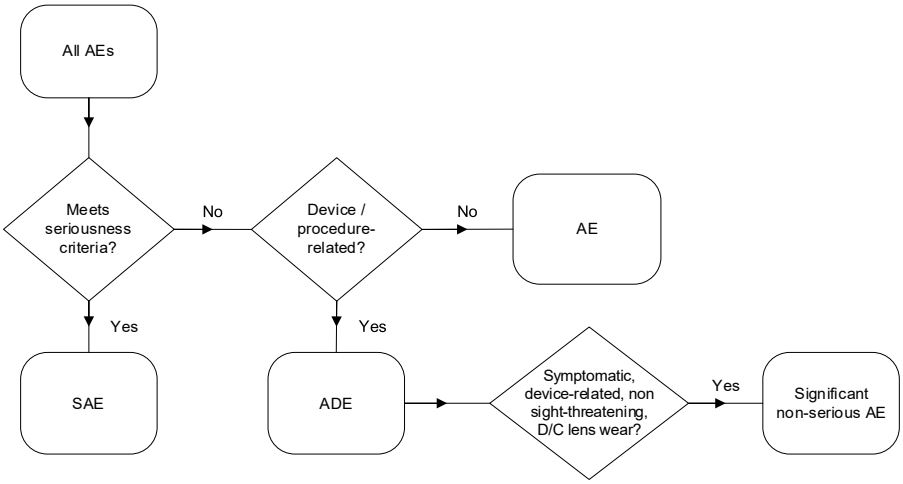
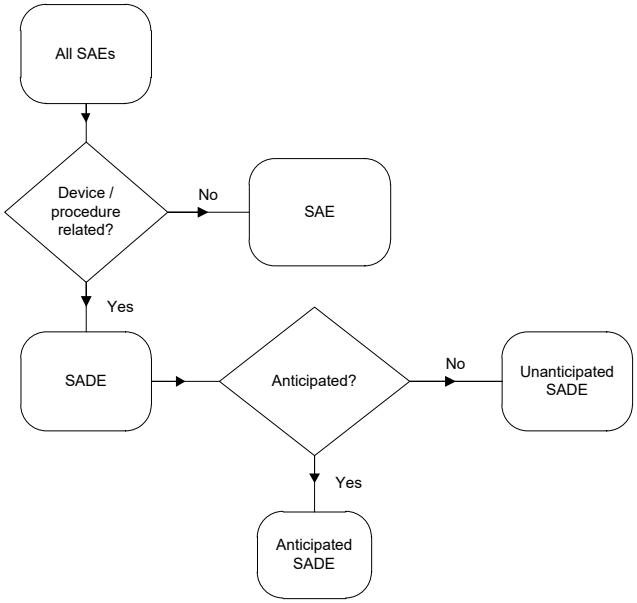


Figure 11–2 Categorization of All Serious Adverse Events



Specific Events Relevant to this Protocol

Serious Adverse Events

In addition to reporting all AEs (serious and nonserious) meeting the definitions, the investigator must report any occurrence of the following as an SAE:

- An ocular infection including a presumed infectious ulcer with any of the following characteristics:
    - Central or paracentral location
    - Penetration of Bowman's membrane
    - Infiltrates >2 mm diameter
    - Iritis
    - Increase in intraocular pressure
    - Culture positive for microorganisms
    - Increasing size or severity at subsequent visits
- Any central or paracentral corneal event (such as neovascularization) that results in permanent opacification
- Hypopyon
- Hyphema
- Neovascularization within the central 6 mm of the cornea
- Permanent vision loss as defined by loss of 2 or more lines of Distance BCVA from enrollment visit that fails to resolve
- Uveitis (anterior, intermediate, or posterior)
- Corneal abrasion affecting ≥50% of corneal surface area

Significant Nonserious Adverse Events

A significant nonserious AE is a device-related, non-sight-threatening adverse event that warrants discontinuation of any contact lens wear for greater than or equal to 2 weeks. In addition, the investigator must report any occurrence of the following as a Significant Nonserious Adverse Event:

- Peripheral nonprogressive noninfectious ulcers
- All symptomatic corneal infiltrative events
- Corneal staining score greater than or equal to grade 3 (Refer to MOP for grading scales)

- Temporary vision loss as defined by loss of 2 or more lines of Distance BCVA from enrollment visit that persists for 2 or more weeks
- Neovascularization score greater than or equal to grade 2 (Refer to MOP for grading scales)

The above events are based on the categories provided in the ISO 11980 and the US FDA Premarket Notification (510(k)) Guidance Document for Daily Wear Contact Lenses.

Device Deficiencies

A device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. A device deficiency may or may not be associated with patient harm (i.e., ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The investigator should determine the applicable category listed in the Device Deficiency eCRF for the identified or suspect device deficiency and report any patient harm separately. Examples of device deficiencies include the following:

- Failure to meet product specifications (e.g., incorrect lens power/diameter/base curve/color)
- Lens/solution cloudy
- Lens surface/edge defect
- Torn lens during handling/in pack
- Packaging deficit (e.g., mislabeled product, tampered seal, leaking bottle/container)
- Suspect product contamination

11.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the standard questions shown below and report as applicable:

- “Have you had any health problems since your last study visit?”
- “Have there been any changes in the medicines you take because of a new health issue since your last study visit?”

In addition, changes in biomicroscopy findings [redacted] evaluated during the study are to be reviewed by the investigator. Any untoward (unfavorable and unintended) change in a biomicroscopy parameter [redacted] that is clinically relevant, in

the opinion of the investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent Any pre-existing medical conditions or signs/symptoms present in a subject prior to the start of the study (i.e., before informed consent is signed) are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

[redacted]

For each recorded event, the ADEs and SAEs documentation must include: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the investigator must document all device deficiencies reported or observed with test and comparator products on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- ADEs or SAEs are documented on the *Serious Adverse Event and Adverse Device Effect* eCRF within 24 hours of the investigator's or site's awareness.
- Device deficiencies are documented on the *Device Deficiency* eCRF within 24 hours of the investigator's or site's awareness.
- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.
- Document all relevant information from Discharge Summary, Autopsy Report,
- Certificate of Death etc., if applicable, in narrative section of the *Serious Adverse Event and Adverse Device Effect* eCRF.

Note: Should the EDC system become nonoperational, the site must complete the appropriate paper *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency* Form. The completed form is emailed to the Study Sponsor at msus.safety@Alcon.com according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for nonstudy marketed devices/products (i.e. CLEAR CARE contact lens solution) will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study Sponsor representatives may be contacted for any protocol related question and their contact information is provided in the Manual of Procedures that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor may request copies of applicable portions of the subject's medical records. The investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

Intensity and Causality Assessments

Where appropriate, the investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the investigator must assess the causality (Related or Not Related to the medical device or study procedure). An assessment of causality will also be performed by Study Sponsor utilizing the same definitions, as shown below:

Causality

Related	An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.

Not Related An AE classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the AE).

The Study Sponsor will assess the AEs and may upgrade the investigator's assessment of seriousness and/or causality. The Study Sponsor will notify the investigator of any AEs that is upgraded from nonserious to serious or from unrelated to related.

11.4 Return product analysis (as applicable)

Study Sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.

Alcon study products associated with device deficiencies and/or product related AEs should be returned and must include the Complaint # which will be provided by Study Sponsor after the case is entered in the Study Sponsor's Global Product Complaint Management System (GPCMS) after the database lock.

11.5 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study (See Section 9.4 for details on the masking procedure). If the treatment code needs to be broken in the interest of subject safety, the investigator is encouraged to contact an appropriate Study Sponsor representative prior to unmasking the information if there is sufficient time. Dependent upon the individual circumstances (i.e., medical emergency), the code may be broken prior to contact with the Study Sponsor. The Study Sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the Study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

11.6 Follow-Up of Subjects with Adverse Events

The investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The investigator should provide the Study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ ongoing at time of discontinuation, any additional information received at follow-up should be documented in the eCRFs up to study completion (i.e., database lock). Any additional data received up to 1 month after subject completed the study should be documented and available upon the Study Sponsor's request.

All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements. The investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

11.7 Pregnancy in the Clinical Study

Women of childbearing potential or women who are pregnant at the time of study entry are not excluded from participation. Pregnancy should be included in the corresponding section of the eCRF (i.e., Pregnancy CRF) when a pregnant woman enters the study or if a woman becomes pregnant during the study. Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case-by-case basis.

12 ANALYSIS PLAN

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized with frequencies and percentages from each category.

Any deviations to this analysis plan will be updated during the course of the study as part of a protocol amendment or will be detailed in the clinical study report.

12.1 Subject Evaluability

The final subject evaluability will be determined prior to breaking of the code for masked treatment (lens sequence) assignment and locking the database, based on the Deviations and Evaluability Plan.

12.2 Analysis Sets

12.2.1 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. As such, the safety analysis set will include all subjects/eyes exposed to any study lenses evaluated in this study. [redacted]

Therefore, any AE or device deficiency occurring after Informed Consent and prior to the initial exposure to the study lenses (test or comparator) under evaluation in this clinical protocol will be listed as pretreatment. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study lenses exposed in the corresponding lens sequence.

12.2.2 Full Analysis Set

The full analysis set (FAS) is the set of all randomized subjects who are exposed to any study lenses evaluated in this study, [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.3 Demographic and Baseline Characteristics

Demographic information will be summarized by lens sequence and overall. Frequencies and percentages will be presented for categorical variables such as sex, age group, race, and ethnicity. Number of observations, mean, SD, median, minimum, and maximum will be presented for continuous variables such as age.

12.4 Effectiveness Analyses

This study defines 1 primar [redacted] effectiveness endpoint [redacted] will use the FAS as the primary analysis set.

[redacted]

[redacted]

[redacted]

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to evaluate visual acuity of the [redacted] Toric soft contact lenses.

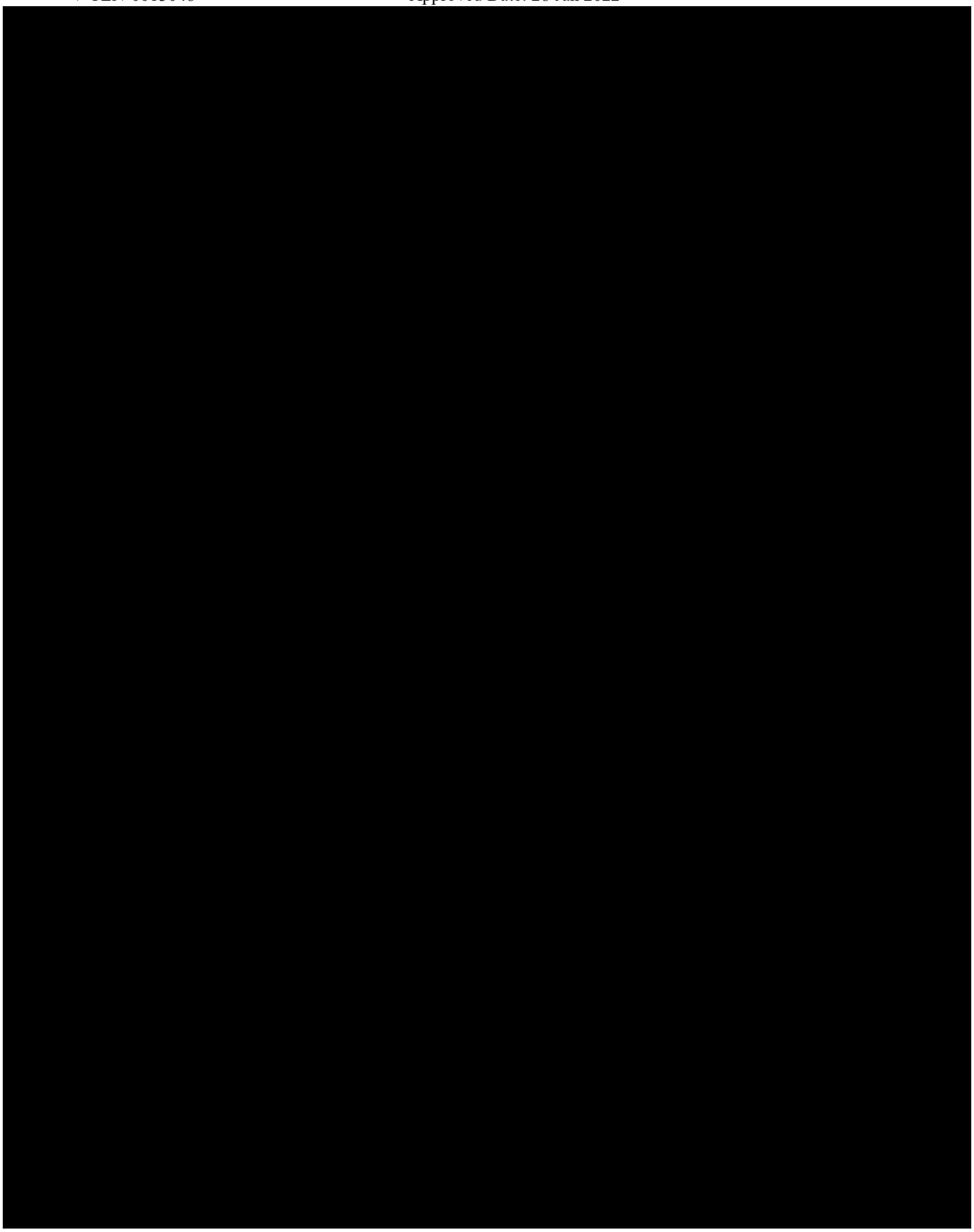
The primary endpoint is distance VA with study lenses, collected for each eye in logMAR.

12.4.1.1 Statistical Hypotheses

No inferences are to be made on the primary effectiveness endpoint; therefore, no hypotheses are formulated.

12.4.1.2 Analysis Methods

Descriptive statistics used for continuous variables will be presented.



[redacted]

12.5 Handling of Missing Data

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out for the primary [redacted] ffectiveness analyses.

12.6 Safety Analyses

The safety endpoints are:

- AEs
- Biomicroscopy findings
- Device Deficiencies

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of adverse events as well as the other listed parameters.

All AEs occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. Descriptive summaries (frequencies and percentages) for ocular and nonocular AEs will be presented by Medical Dictionary for Regulatory Activities Preferred Terms. AEs leading to study discontinuation, significant nonserious AEs, and SAEs will be identified. Individual subject listings will be provided, as necessary.

Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to IP.

Each biomicroscopy parameter will be tabulated by its grade. For each biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 2 grades from baseline (last assessment prior to study lens exposure) to any subsequent visit within the same period will be presented. A supportive listing will be generated which will include all biomicroscopy data from all visits within the same period for those eyes experiencing the increase.

Two listings for device deficiencies, prior to exposure to study contact lenses and treatment-emergent, will be provided. Additionally, each device deficiency category will be tabulated.

No inferential testing will be conducted for the safety analyses.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The investigator must ensure that the subject's identity is kept confidential throughout the course of the study. In particular, the investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. The study sponsor may collect a copy of the enrollment log ***without any directly identifying subject information***.

The study sponsor may share patient-level data collected in this trial with qualified researchers to help facilitate product development or enhancements in research that is not directly related to the study objectives. The Informed Consent explains this to the study subject.

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor,

and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the study sponsor and are independent of study site staff.

If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility
- Date of informed consent
- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Only designated individuals at the site will complete the CRFs. The CRFs must be completed at regular intervals following the clinical study visit schedule. It is expected that all data reported have corresponding entries in the source documents. The principal investigator is responsible for reviewing and certifying that the CRFs are accurate and complete. The only subject identifiers recorded on the CRFs will be subject number, and subject demographic information.

13.3 Data Review and Clarifications

A review of CRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the CRFs have been completed, additional data clarifications and/or additions may be needed as a result of the data cleaning process. Data clarifications are documented and are part of each subject's CRF.

13.4 Sponsor and Monitoring Responsibilities

The study sponsor will select principal investigators that are qualified by education, training, and experience to assume responsibility for the proper conduct of this clinical trial.

The study sponsor is financially funding this clinical trial and will compensate the investigator and/or the Institution(s) at which the study is conducted in accordance with a signed clinical trial agreement.

The study sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals according to the study monitoring plan. The clinical investigation will be monitored to ensure that the rights and well-being of the subjects are protected, the reported data are accurate, complete, and verifiable from the source documents, and the study is conducted in compliance with the current approved protocol (and amendments[s], if applicable), with current GCP, and with applicable regulatory requirements.

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate study sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

A coordinating investigator may be identified by the study sponsor to review and endorse the final study report. In cases where a coordinating investigator is engaged, the study sponsor will select the coordinating investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

13.5 Regulatory Documentation and Records Retention

The investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the study sponsor and the investigator’s files will be reviewed as part of the ongoing study monitoring. Financial information is to be kept separately.

Additionally, the investigator must keep study records and source documents consistent with the terms of the clinical study agreement with the study sponsor. If the investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, then the study sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

13.6 Quality Assurance and Quality Control

The study sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the study sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the study sponsor with the investigator/institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

Investigations are conducted in compliance with Good Clinical Practices; international and national regulations, laws and guidelines; the conditions of approval imposed by reviewing IRBs/IECs or regulatory authorities; and in accordance with the ethical medical research principles outlined in the Declaration of Helsinki.

- The SOPs of the study sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations shall apply.
- Notifications and timelines for reporting protocol deviations should be based upon applicable Ethics Committee requirements.

The investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. Deviations from this protocol, regulatory requirements, and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The investigator must provide documentation of the IRB/IEC approval to the study sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the Package Insert, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the study, the investigator must notify the IRB/IEC about the study's completion. The

IRB/IEC also must be notified if the study is terminated prematurely. Finally, the investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject. The obtaining of consent shall be documented before any procedure specific to the clinical investigation is applied to the subject.

The investigator must have a defined process for obtaining the required consent. Specifically, the investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the investigator, and if required by local regulation, other qualified personnel. The investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and sponsor-designated personnel. The investigator must keep the original, signed copy of the consent (file in subject's medical records) and must provide a duplicate copy to each subject according to local regulations.

The study sponsor assures that the key design elements of this protocol will be registered on www.clinicaltrials.gov if required by current regulations and, if applicable, other public databases as required by local country regulations. In addition, results of this study will be made publicly available on www.clinicaltrials.gov regardless of outcome if required by current regulations and, if applicable, in other public databases as required by local country regulations.

15 REFERENCES

15.1 Regulations and Standards

The following references may be applicable in whole or in part for this clinical trial.

- 21 CFR Part 11 - Electronic Records; Electronic Signatures

- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- The California Bill of Rights, if applicable

15.2 Scientific and Other References

Not applicable. There are no references.