

Clinical Performance Evaluation of Two Frequent
Replacement Silicone Hydrogel Multifocal Toric Contact
Lenses

STUDY ID:
CLR624-C001

PROTOCOL v.2
August 01, 2024

NCT06461455



Device Protocol for CLR624-C001

**Title: Clinical Performance Evaluation of Two Frequent Replacement
Silicone Hydrogel Multifocal Toric Contact Lenses**

Protocol Number:	CLR624-C001
Clinical Investigation Type:	Pivotal
Test Product:	TOTAL30 Multifocal for Astigmatism
Sponsor Name and Address:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099



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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:

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1 GLOSSARY OF TERMS

Names of Test Product(s)	Throughout this document, test product TOTAL30 Multifocal for Astigmatism will be referred to as T30 MFfA.
Name of Comparator Product(s)	Throughout this document, comparator product ULTRA [®] Multifocal for Astigmatism will be referred to as ULTRA MFfA.
Adverse Device Effect (ADE)	<p>Adverse event related to the use of an investigational medical device or comparator.</p> <p><i>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.</i></p>
Adverse Event (AE)	<p>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 or comparator and whether anticipated or unanticipated.</p> <p><i>Note: For subjects, 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 the use of the investigational medical device or comparator.</i></p> <p>Requirements for reporting adverse events in the study can be found in Section 11.</p>
Anticipated Serious Adverse Device Effect (ASADE)	An effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

Clinical Investigation Plan (CIP)	<p>The document(s) stating the rationale, objectives, design, and prespecified analysis, methodology, organization, monitoring, conduct, and record-keeping of the clinical investigation.</p> <p><i>Note: The protocol and other documents referenced in the protocol (for example, the SAP, the MOP, the DEP, and the Protocol Monitoring Plan) comprise the CIP.</i></p>
Clinical Investigation Report (CIR) / Clinical Study Report	<p>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.</p>
Device Deficiency	<p>Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.</p> <p><i>Note: This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling related to the investigational medical device or the comparator.</i></p> <p>Requirements for reporting device deficiencies in the study can be found in Section 11.</p>
Enrolled Subject	<p>Any subject who signs an informed consent form for participation in the study.</p>
Point of Enrollment	<p>The time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form.</p>
Interventional Clinical Trial	<p>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.</p>

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).
Noninterventional Study	<p>Clinical investigation that draws inferences about the possible effect of an intervention on subjects, but the investigator has not assigned subjects into intervention groups based on a protocol and has not made any attempts to collect data on variables beyond those available throughout the course of normal clinical practice and burden to the subject.</p> <p>NOTE: The term "noninterventional" is synonymous with "observational."</p>
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Product Complaint	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling, or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.
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)	<p>Adverse event that led to any of the following:</p> <ul style="list-style-type: none">• Death.• A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:<ul style="list-style-type: none">a) a life-threatening illness or injury <i>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.</i>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. <p><i>Note: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.</i></p> <p><i>Refer to Section 11 for additional SAEs.</i></p>
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Serious Health Threat	<p>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.</p> <p><i>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.</i></p>
Significant Nonserious Adverse Event	<p>A significant nonserious adverse event is 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.</p> <p><i>Refer to Section 11 for additional significant nonserious AEs.</i></p>
Study Start	<p>The start of the study is considered to coincide with the enrollment of the first patient.</p>
Study Completion	<p>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.</p>
Unanticipated Serious Adverse Device Effect (USADE)	<p>Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk assessment.</p>

Use Error	<p>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.</p> <p><i>Note:</i></p> <ul style="list-style-type: none"><i>a) Use error includes the inability of the user to complete a task.</i><i>b) Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.</i><i>c) Users might be aware or unaware that a use error has occurred.</i><i>d) An unexpected physiological response of the patient is not by itself considered a use error.</i><i>e) A malfunction of a medical device that causes an unexpected result is not considered a use error.”</i>
Vulnerable Subject	<p>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.</p>

2 LIST OF ACRONYMS AND ABBREVIATIONS

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

Abbreviation	Definition
ADD	Addition
ADE	Adverse device effect
AE(s)	Adverse event(s)
ASADE	Anticipated serious adverse device effect
██████	████████████████████
CFR	Code of Federal Regulations
CI	Confidence intervals
CIP	Clinical investigation plan
CIR	Clinical investigation report
██████	████████████████████
CLs	Confidence limits
cm	centimeter(s)
COL	Clinical operations lead
CRF	Case report form
CSM	Clinical study manager
D	Diopter
DEP	Data evaluability plan
ECP	Eye care professional
eCRF	Electronic case report form
EDC	Electronic data capture
EN	European Standard
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HC/HI	High contrast/high illumination
HI	High
Hrs	Hours
IB	Investigator’s brochure
ICF	Informed consent form
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
LCL	Lower confidence limit
LO	Low
logMAR	Logarithm of the minimum angle of resolution
M	Meter
MED	Medium
min	minute(s)
mm	millimeter
MOP	Manual of procedures
████	████████████████
N	Number of subjects
N/A	Not applicable

Abbreviation	Definition
NI	Noninferiority
OD	Right eye
OS	Left eye
OU	Both eyes
PI	Principal investigator
PP	Per protocol
pt	point
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SLE	Slit lamp examination
SOP	Standard operating procedure
T30 MFfA	TOTAL30 Multifocal for Astigmatism; LID230451
UCL	Upper confidence limit
ULTRA MFfA	ULTRA Multifocal for Astigmatism
US	United States
USADE	Unanticipated serious adverse device effect
VA	Visual acuity

	<div><div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div><div></div></div><div><div></div><div></div><div></div></div></div> <p>The safety objective of this study is to describe the safety profile of the study products.</p>
Endpoint(s)	<p>Primary effectiveness</p> <ul style="list-style-type: none">Binocular high contrast/high illumination (HC/HI) VA (logMAR) at distance (4 m) at Day 30 with study lenses <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div></div>

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Assessment(s)	Effectiveness
	<ul style="list-style-type: none"> HC/HI logMAR VA at distance (4 m; OD/OS/OU)

	<ul style="list-style-type: none">■ [REDACTED] [REDACTED] [REDACTED]■ [REDACTED] [REDACTED] [REDACTED]■ [REDACTED] [REDACTED]■ [REDACTED]■ [REDACTED]<ul style="list-style-type: none">■ [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED] [REDACTED]<ul style="list-style-type: none">■ [REDACTED]■ [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]■ [REDACTED]■ [REDACTED]■ [REDACTED] [REDACTED]■ [REDACTED]
--	--




	Safety <ul style="list-style-type: none">• Adverse events• Biomicroscopy• Device deficiencies
Study Design	This is a prospective, randomized [REDACTED] bilateral, crossover, double masked (study lenses), dispensing study. Subjects will be expected to attend 5 office visits and will be dispensed study lenses (T30 MFfA and ULTRA MFfA lenses) for a 30-day duration of bilateral wear each (total of 60 days of lens wear), with a washout period (wearing habitual spectacles) of 2-3 days (at least 48 hours) prior to each dispense visit.
Subject population	<ul style="list-style-type: none">• Age and habitual wear consideration: The subject population consists of volunteer subjects aged ≥ 40 years, who are habitual biweekly/monthly replacement soft multifocal or multifocal toric contact lens wearers for at least past 3 months and wear their habitual lenses at least 5 days per week and at least 8 hours per day. <ul style="list-style-type: none">■ [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]■ [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]■ [REDACTED] [REDACTED] [REDACTED]

	<p>Planned number of subjects enrolled/consented: approximately 82</p> <p>Planned number of completed subjects: 74</p>
Sites and Locations	<p>Planned number of clinical sites: approximately 8</p> <p>Planned locations (initial list of locations, which may change during start up or conduct according to study needs): US</p>
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	<ul style="list-style-type: none">• Habitual biweekly/monthly replacement soft multifocal or multifocal toric contact lens wearers aged ≥ 40 years• Habitual wearer in both eyes for a minimum of 5 days per week and 8 hours per day during the past 3 months• Manifest cylinder ≥ 0.75 D in each eye at Screening• Willing to wear the study contact lenses for at least 8 hours per day during the treatment period and for at least 12 hours on the day before each Day 30 Follow-Up Visit• Subject must be willing to not use readers while wearing study contact lenses for duration of the study
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	<ul style="list-style-type: none">• Any use of topical ocular medications and artificial tear or rewetting drops that would require instillation during contact lens wear• 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• Monovision contact lens wearers and wearers of contact lens in one eye only

Data analysis and sample size justification	Planned Data Analysis		
	To address the primary effectiveness [REDACTED] planned inferential analyses are summarized below:		
	Endpoint	Comparison	Statistical Model
	Primary		
	Binocular HC/HI VA at Distance	T30 MFfA vs ULTRA MFfA NI*	Mixed effects repeated measures NI margin = 0.05 (logMAR)
[REDACTED]			

	<div data-bbox="634 180 1404 506"></div> <div data-bbox="669 531 836 569">Sample Size</div> <div data-bbox="669 598 1321 678">Sample size calculation is based on a prior feasibility clinical study <div data-bbox="846 653 1252 678"></div></div> <div data-bbox="634 684 1404 968"></div>
Associated materials	<ul style="list-style-type: none">• Subjects will be provided with CLEAR CARE® Cleaning & Disinfecting solution.• Lubrication/rewetting drops will not be permitted during study lens wear. However, habitual lubrication/rewetting drop usage is allowed up to 10 minutes prior to lens insertion and any time after lens removal during the study.• Lubrication/rewetting drops during clinic visits will only be administered per investigator discretion.• LacriPure saline will be permitted for rinsing the lens(es) after removal and prior to insertion, if required.

Table 3–1 **Schedule of Study Procedures and Assessments**

	 Visit 1 Screening/ Baseline/ Fit	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
		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		
		Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)	Day 30 (-2/+1 days)	Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)	Day 30 (-2/+1 days)		
Procedure							
Informed consent	X						
Demographics	X						
Medical history [∞]	X	X	X	X	X	X	X
Concomitant medications [∞]	X	X	X	X	X	X	X
Habitual lens information (brand, power*, lens care*)	X						
							
V/A with habitual spectacles correction (OD, OS, Snellen distance)*	X				X	(X)	X
Keratometry (OD, OS)	X						

	Visit 1 Screening/ Baseline/ Fit	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
		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		
Procedure		Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)	Day 30 (-2/+1 days)	Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)	Day 30 (-2/+1 days)		
Autorefractometry (OD, OS, uncorrected or with study lenses)	X uncorrected		X with study lenses		X with study lenses		X with study lenses
Manifest refraction	X	(X)	(X)	(X)	(X)	(X)	(X)
	■	■	■	■	■	■	■
Biomicroscopy	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X						
Randomization	X						
	■						

	Visit 1 Screening/ Baseline/ Fit	LENS 1 (Period 1)		LENS 2 (Period 2)		Unscheduled Visit	Early Exit
		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		
Procedure		Day 1 (Visit 2 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 1)	Day 30 (-2/+1 days)	Day 1 (Visit 4 must occur after washout with habitual spectacles, 2 to 3 days [at least 48 hours] after the end of Visit 3)	Day 30 (-2/+1 days)		
Collect worn lenses*			X		X	(X)	X
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

∞ Concomitant medications and medical history must be fully documented and collected in the subject source documents with targeted collection in the EDC.

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.

5 INTRODUCTION

5.1 Rationale and Background

Presbyopia is a refractive error condition that develops as part of normal aging in which the natural crystalline lens of the eye progressively loses the focusing ability, resulting in difficulty at focusing for close objects and for activities like reading. The signs of presbyopia become noticeable around the age of 40 years. Presbyopia may be corrected with single-vision, bifocal or progressive spectacles, progressive addition lenses, monovision contact lenses or multifocal contact lenses.

Astigmatism is a refractive error condition that describes when the curvature of the cornea and/or lens inside the eye is imperfect, i.e., not perfectly curved. Common symptoms of astigmatism include blurry vision and specifically, blurry vision occurring more in one direction than another, a symptom that is commonly observed when looking at headlights at night. One can be born with astigmatism, or it may be developed after birth. Common corrections for astigmatism include spectacles, toric contact lenses, and refractive surgery.

To address the growing needs of a presbyopic population with astigmatism, T30 MFfA soft contact lenses, which is intended to be a monthly replacement water gradient contact lens, has been developed. These multifocal toric lenses use the Alcon Precision Profile® center-near aspheric multifocal design and the Alcon Precision Balance 8|4® ballast toric design, which have been successfully adopted for TOTAL30® for Presbyopia and TOTAL30® for Astigmatism, respectively.

TOTAL30 Multifocal for Astigmatism (T30 MFfA) is intended for daily wear (with removal for daily cleaning and disinfection) for the optical correction of refractive ametropia (myopia

and hyperopia) in persons with nondiseased eyes who require a reading addition of +3.00 D or less and who have astigmatism.

The lenses are intended for daily wear (less than 24 hours while awake) with removal for disposal, or cleaning and disinfection (chemical, not heat) prior to reinsertion, as recommended by an eye care professional. Lenses should be discarded and replaced with a new pair after one month or more often, if recommended by an eye care professional.

The T30 MFfA contact lens possesses unique material properties and inherently wettable core material with a water gradient surface to provide sustained long-lasting performance. These 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 T30 MFfA contact lens will be assessed and compared to the commercially available ULTRA MFfA 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 study will compare the clinical performance of T30 MFfA contact lenses with ULTRA MFfA. [REDACTED]

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

There are no immediate plans to submit the results of this study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing.

5.3 Risks and Benefits

Risk management principles have been applied to both the planning and the intended conduct of the clinical investigation, in order to ensure the reliability of the clinical data generated and the safety of the subjects. 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 test product. 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 IB for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective

Table 6–1 Primary Objective

<u>Objective</u>	<u>Endpoint</u>
The primary objective of this study is to demonstrate NI in VA at distance when wearing T30 MFfA lenses compared to ULTRA MFfA lenses, after 30 days of wear (Day 30).	Binocular HC/HI VA (logMAR) at distance (4 m) at Day 30 with study lenses

6.2 Secondary Objective

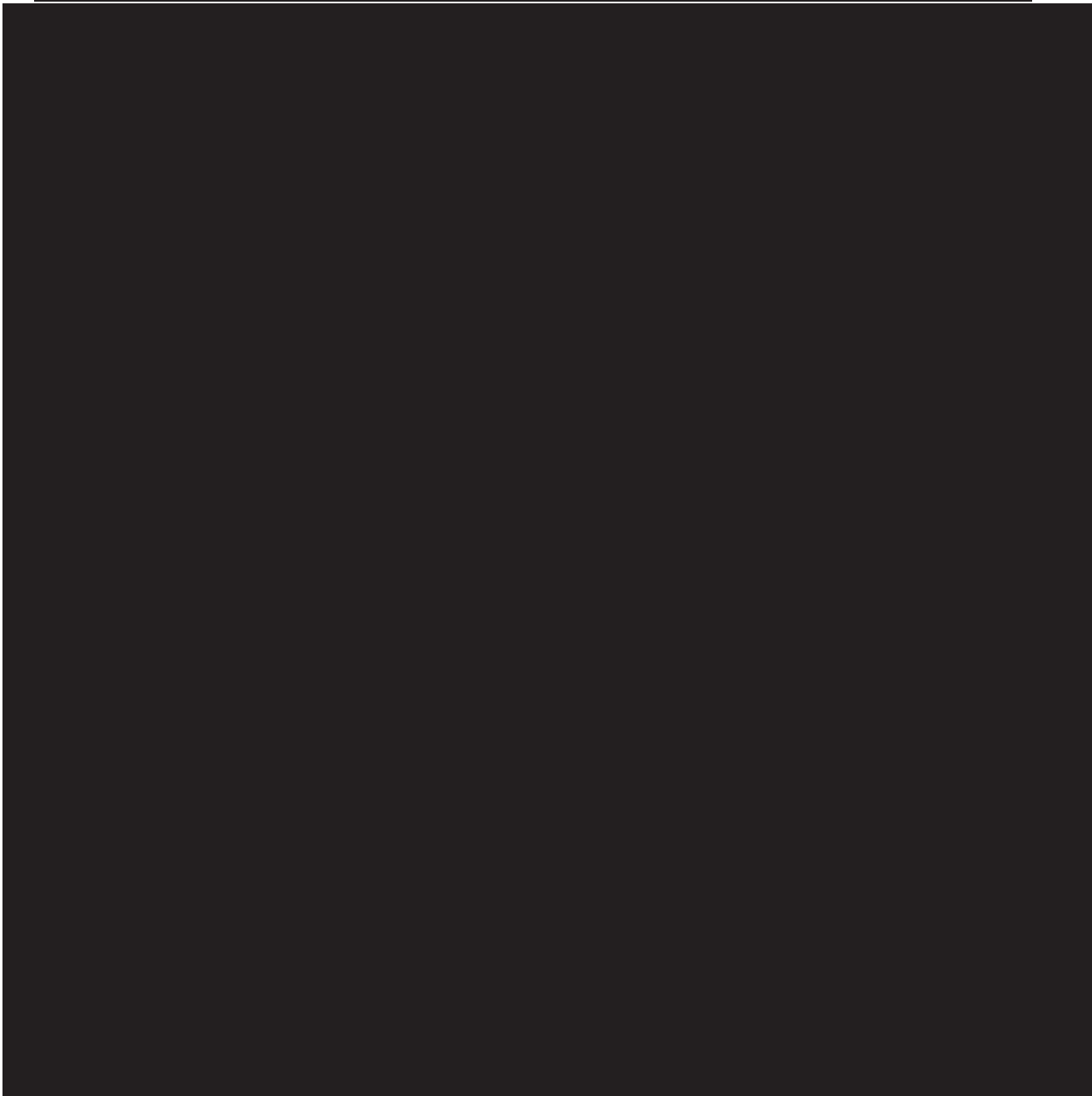
Not applicable.











6.4 Safety Objective

Table 6–3 Safety Objective

<u>Objective(s)</u>	<u>Endpoint(s)</u>
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The safety objective of this study is to 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 [REDACTED] dispense, double masked, bilateral, crossover study comparing 2 reusable multifocal toric soft contact lenses. The expected duration of subject participation in the study is approximately 66 days (~30 days for each lens type with 2 to 3 days (at least 48 hours) of washout prior to each lens period), with 5 scheduled visits. Subjects will be asked to wear their habitual spectacles only (no contact lens wear) during the washout periods after Visit 1 and after Visit 3. Subjects will be asked to wear their study lenses for at least 8 hours a day during the lens wear period and for at least 12 hours on the day prior to each follow-up visit (Visits 3 and 5).



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 wearing period. Therefore, [REDACTED] [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 multifocal contact lenses in both eyes during the past 3 months for a minimum of 5 days per week and 8 hours per day. This will avoid confounding safety responses in non-adapted subjects. Habitual ULTRA MFfA and ULTRA for Presbyopia contact lens wearers are allowed to participate in this trial and may constitute up to approximately 50% of the total subject population. The study will exclude subjects who are monovision contact lens and wearers of contact lens in one eye only.

Lubrication/rewetting drops will not be permitted during study lens wear, as this may confound the primary effectiveness and key exploratory variables. However, habitual lubrication/rewetting drop usage is allowed up to 10 minutes prior to lens insertion and any time after lens removal during the study.

Currently pregnant or lactating women and participants with any history of amblyopia, strabismus or binocular vision abnormalities will be excluded from the trial, to prevent confounding the safety/effectiveness endpoints. Subjects who become pregnant during the study will not be discontinued; however, data will be excluded from the effectiveness analyses because pregnancy can alter refraction and VA results.

7.3 Rationale for Duration of Treatment/Follow-up

The primary [REDACTED] will be assessed on Day 30. Additionally, the product is intended for daily wear with monthly replacement. Therefore, subjects will wear each study product bilaterally for approximately 30 days.

7.4 Rationale for Choice of Comparator Product

ULTRA MFfA contact lenses are chosen for the comparator product because these lenses have the same wear modality and monthly replacement schedule as T30 MFfA lenses. Additionally, ULTRA MFfA's intended use and intended population are similar to T30 MFfA's.

7.5 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population consists of male and female subjects 40 years old and above with a diagnosis of both presbyopia and astigmatism. It is aimed to enroll (consent) approximately 82 subjects in approximately 8 sites in the US, with a target of 74 total subjects completed, with approximately 10 (intended minimum) to 12 (intended maximum) subjects per site. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 5 weeks; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol. Because an approximately 5% screening failure rate and 5% discontinue rate is expected, approximately 82 subjects are expected to be enrolled.

This protocol allows enrollment of the following vulnerable population(s), with associated justification for each population:

Elderly (age 65 years or above) – Presbyopia and associated gradual loss of accommodation is part of the aging process and worsens with increasing age. Multifocal contact lenses are a commonly used correction option for this condition. The contact lens under study is intended to alleviate this condition. Therefore, it is appropriate and necessary to include elderly subjects in this clinical trial to gain data regarding the safety and effectiveness of the T30 MFfA contact lenses in this population. Elderly subjects will be protected through the informed consent process, which will include any risks specific to the elderly subjects, as well as any specific responsibilities associated with their participation. In addition, an IRB/IEC will review and approve the inclusion of elderly subjects in this clinical trial prior to enrollment of elderly subjects. Any specific requirements imposed by the IRB/IEC regarding participation of elderly subjects will be implemented and documented, as appropriate. Upon conclusion of the clinical trial, all subjects, including elderly subjects, will return to standard medical care for ongoing conditions.

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. Subject must be able to understand and sign an IRB/IEC approved informed consent form.
2. Subject must be willing and able to attend all scheduled study visits as required per protocol.

3. Subject must be at least 40 years of age at Screening.
4. Subject must be willing to stop wearing their habitual contact lenses for the duration of study participation.
5. Subject must be a current wearer of biweekly/monthly replacement multifocal or multifocal toric soft contact lenses in both eyes for a minimum of 5 days per week and 8 hours per day during the past 3 months.
6. Manifest cylinder ≥ 0.75 D in each eye at Screening.
7. BCVA distance (as determined by manifest refraction at Screening) 20/25 or better in each eye with a spherical refractive error in the range of the provided parameters of the study and requiring a near ADD of +0.75 to +2.50 D in each eye.
8. Subject must be willing to wear the study contact lenses for at least 8 hours per day during the treatment period and for at least 12 hours on the day before each Day 30 Follow-Up Visit.
9. Subject must possess spectacles and be willing to wear habitual spectacles for vision correction when study lenses are not worn, as needed.
10. Subject must be willing to not use readers while wearing study contact lenses for duration of the study.

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 planning 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, and/or the presence of corneal infiltrate.
6. Current or history of pathologically dry eye in either eye that, in the opinion of the investigator, 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. Currently pregnant or lactating, as stated by subject at Screening.
11. Any history of amblyopia, strabismus, or binocular vision abnormalities.
12. Any use of topical ocular medications and artificial tear or rewetting drops that would require instillation during contact lens wear.
13. 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.
14. Participation of the subject in a clinical trial within the previous 30 days or currently enrolled in any clinical trial.
15. Monovision contact lens wearers and wearers of contact lens in one eye only.
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)

<i>Test Product(s):</i>	TOTAL30 Multifocal for Astigmatism (T30 MFfA); LID230451
<i>Comparator Product(s)</i>	ULTRA Multifocal for Astigmatism (ULTRA MFfA)

Table 9–1 Test Product

Test Product	TOTAL30 Multifocal for Astigmatism (T30 MFfA); LID230451
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Regulatory/Market Status	Regulatory/Market Status of Product at Time of Protocol Approval US: Product has received FDA 510(k) clearance; not yet marketed.
Indication for use and intended purpose in the current study	<p>TOTAL30 Multifocal for Astigmatism (lehfilcon A) soft contact lenses are indicated for the optical correction of presbyopia with or without refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes who may require a reading addition of +3.00 D or less and who may have up to 6.00 D of astigmatism.</p> <p>The lenses are to be prescribed for daily wear with removal for cleaning and disinfection prior to reinsertion, or disposal, as recommended by the eye care professional. Lenses should be discarded and replaced with a new pair each month, or more often if recommended by an eye care professional.</p>
Product description and parameters available for this study	<ul style="list-style-type: none">• Material: lehfilcon A• Water content: 55 ± 2 %• Power range: Limited lens parameters of the investigational product will be provided: Sphere: -1.25 to -3.00 D in 0.25 D steps Cylinder: -0.75 D, -1.25 D

	<p>Axis: 080°, 090°, 100°, 180° ADD: LO, MED, HI Note: The following power combinations will not be included in the study:</p> <ul style="list-style-type: none"> • Sphere -1.50 D, Cylinder -1.25 D, Axis 180°, ADD HI • Sphere -2.00 D, Cylinder -0.75 D, Axis 090°, ADD LO <p>Sphere: -1.00 D Cylinder: -0.75 D Axis: 080°, 090°, 100°, 180° ADD: LO, MED, HI</p> <p>Sphere: +1.00 to +4.00 D in 1 D steps Cylinder: -0.75 D Axis: 080°, 090°, 100°, 180° ADD: LO, MED, HI</p> <ul style="list-style-type: none"> • Base curve (mm): 8.6 • Diameter (mm): 14.5
Formulation	N/A
Usage	<ul style="list-style-type: none"> • Wear: <ul style="list-style-type: none"> ○ Daily wear ○ Bilateral • Replacement period: monthly replacement, daily wear • Exposure: Study lenses are to be worn during typical contact lens wearing hours, for at least 8 hours per day, every day during the 30-day period. Subjects will be asked to wear their study lenses for at least 12 hours on the day before their Day 30 Follow-up Visit. • Lens Care: Subjects will be provided with CLEAR CARE® Cleaning & Disinfecting Solution for cleaning and disinfecting the study lenses after each use.
Number/Amount of product to be provided to the subject	<p>Lenses (to be used for fitting and study lens wear) will be provided in bulk by the sponsor. Subjects will be dispensed one pair of study lenses at the Dispense Visit. No spare lenses will be provided to the subjects.</p> <p>If a replacement lens(es) is required, the subject must return to the clinic for an unplanned lens replacement. Until the replacement</p>

	lens(es) is obtained, the subject must store both study lenses as instructed. Refer to MOP for detailed instructions.
Packaging description	Blister foil pack
Labeling description	<p>Lens foil label includes:</p> <ul style="list-style-type: none"> • material name and identifier • base curve • diameter • packing solution • power • lot number • expiration date • content statement • investigational device statement • sponsor information <p>Lens inventory will be provided in packages and identified with the following:</p> <ul style="list-style-type: none"> • a color-coded label stating the study protocol number/LID number • power • an investigational use only statement • handling unit/tracking 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	Test lenses will be provided by the sponsor. Refer to the MOP for a detailed description.

Table 9–2 **Comparator Product**

Comparator Product(s)	ULTRA Multifocal for Astigmatism (ULTRA MFfA)
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Manufacturer	Bausch and Lomb
Regulatory/Market Status	Regulatory/Market Status of Product at Time of Protocol Approval US: Product approved; product marketed
Indication for Use	Refer to package insert
Product description and parameters available for this study	<ul style="list-style-type: none"> Material: samfilcon A Water content: 46% Power range: Limited ULTRA MFfA parameters will be used in this study: <ul style="list-style-type: none"> Sphere: -1.00 to -3.25 D in 0.25 D steps Cylinder: -0.75 D, -1.25 D Axis: 080°, 090°, 100°, 180° ADD: Low, High Sphere: -0.75 to -1.25 D in 0.25 D steps Cylinder: -0.75 D Axis: 080°, 090°, 100°, 180° ADD: Low, High Sphere: +0.75 D, +1.00 D, +1.25 D, +1.75 D, +2.00 D, +2.25 D, +2.75 D, +3.00 D, +3.25 D, +3.75 D, +4.00 D Cylinder: -0.75 D Axis: 080°, 090°, 100°, 180° ADD: Low, High Base curve (mm): 8.6 Diameter (mm): 14.5
Formulation	N/A
Usage	<ul style="list-style-type: none"> Wear: <ul style="list-style-type: none"> Daily wear Bilateral Replacement period: monthly replacement, daily wear Exposure: Study lenses are to be worn during typical contact lens wearing hours, for at least 8 hours per day, every day during the 30-day period. Subjects will be asked to wear their

	<p>study lenses for at least 12 hours on the day before their Day 30 Follow-up Visit.</p> <ul style="list-style-type: none">• Lens care: Subjects will be provided with CLEAR CARE® Cleaning & Disinfecting Solution for cleaning and disinfecting the study lenses after each use.
Number/Amount of Product to be Provided to the subject	<p>Sites will be using commercially available ULTRA MFfA Fitting Set lenses (to be used for fitting and study lens wear). Subjects will be dispensed one pair of study lenses at the Dispense Visit. No spare lenses will be provided to the subjects.</p> <p>If a replacement lens(es) is required, the subject must return to the clinic for an unplanned lens replacement. Until the replacement lens(es) is obtained, the subject must store both study lenses as instructed. Refer to MOP for detailed instructions.</p>
Packaging description	Commercial packaging
Labeling description	Commercial labeling
Training and/or experience requirements for device	No additional training or experience is required to administer the comparator.
Storage conditions	Refer to Package Insert
Additional identifying information	N/A
Supply	Sites will procure ULTRA MFfA Fitting Sets, as needed. Refer to the MOP for details.

More information on the test product can be found in the investigator's brochure; information on the comparator product can be found in the Package Insert for ULTRA MFfA.

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

During the clinical study, additional medical devices and/or medications that are required in conjunction with the treatment include the following:

- CLEAR CARE Cleaning & Disinfecting Solution: Subjects will be provided CLEAR CARE Cleaning & Disinfecting Solution in commercial packaging with provided instructions.

9.3 Treatment Assignment/Randomization

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/sequences to randomization numbers in the specified ratio. Subjects will be assigned treatment (lens sequence) 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 system to one of the treatments (lens sequences). The investigator or 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 (lens sequence) to be dispensed to the subject.

9.4 Treatment Masking

This study is double masked (study lenses), with subjects randomized to use T30 MFfA or ULTRA MFfA for the duration of 30-days per treatment period. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]



Masked study personnel must avoid seeking information that may compromise masking. Unmasked study personnel must not disseminate information that is potentially unmasking to any masked personnel. The masked and unmasked site personnel must coordinate all study activities as necessary to protect masking and minimize bias during the study.

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. During the study, unmasked designated study staff must provide the IPs to the subjects in accordance with their randomization assignment. 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

Study-specific procedures and assessments described here may include standard of care; other standard of care procedures performed in the clinical management of the subject are not excluded.

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. Refer to the MOP for details.

10.2.2 Medical History and Concomitant Medications

Fully document concomitant medications (taken within the past 30 days prior to the screening visit) and medical history (within 1 year prior to the screening visit) in the subject source documents. 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.

10.2.4 Habitual Lens Information

At Visit 1, the subject's habitual contact lens information will be collected. Refer to the MOP for details.

10.2.5 Keratometry

Keratometry is required at Visit 1. Refer to the MOP for details.

10.2.6 Autorefractometry

Autorefractometry (OD, OS) will be performed either uncorrected or with the study contact lenses. Refer to the MOP for details.

10.2.7 VA with Habitual Correction

VA (Snellen distance; OD, OS) with the subject's habitual spectacles correction will be collected at Visit 1 and at the Exit Visit (Visit 5 or Early Exit) and is optional for Unscheduled Visit. Refer to the MOP for details.

10.2.8 Fitting of Study Products with Fitting Lenses: Effectiveness Assessment

Fitting of study products will be performed for both the test and comparator study lenses at Visit 1 per the randomization assignment. [REDACTED]

[REDACTED]

10.2.10 HC/HI VA with Study Lenses: Effectiveness Assessment

HC/HI logMAR [REDACTED] VA with study lenses will be performed at Visits 2, 3, 4, 5, and Early Exit and is optional at Unscheduled Visit. Refer to the MOP for details.



10.2.18 Worn Lens Collection

Worn lenses will be collected and returned. Refer to the MOP for details.

10.2.19 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.

10.2.20 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 in the subject source documents. See Section 11 for further details regarding AE collection and reporting.

10.2.21 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.

10.2.22 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
- [REDACTED]
- Record changes in medical condition or concomitant medication
- Biomicroscopy

■ [REDACTED]

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](#) and Section [10.5.3](#) as possible.

10.4 Unplanned Lens Replacement

No spare lenses will be dispensed to the subject. If a lens is lost, damaged, or needs to be replaced due to a device deficiency/ADE, the subject will be instructed to return for an unplanned lens replacement. Refer to the MOP for details.

10.5 Discontinued Subjects

10.5.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to randomization to product/dispense of study product are considered screen failures. The investigator must document the reason for screen failure in the subject's case history source documents.

Subject numbers must not be reused.

10.5.2 Discontinuations

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

Subject numbers of discontinued subjects must not be reused (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](#) and Section [10.5.3](#), 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.

10.5.3 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](#) and the MOP for details.

10.6 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:

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

10.6.1 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. Refer to the Glossary of Terms and the figures below for categories of AEs and SAEs.

Figure 11-1 Categorization of All Adverse Events

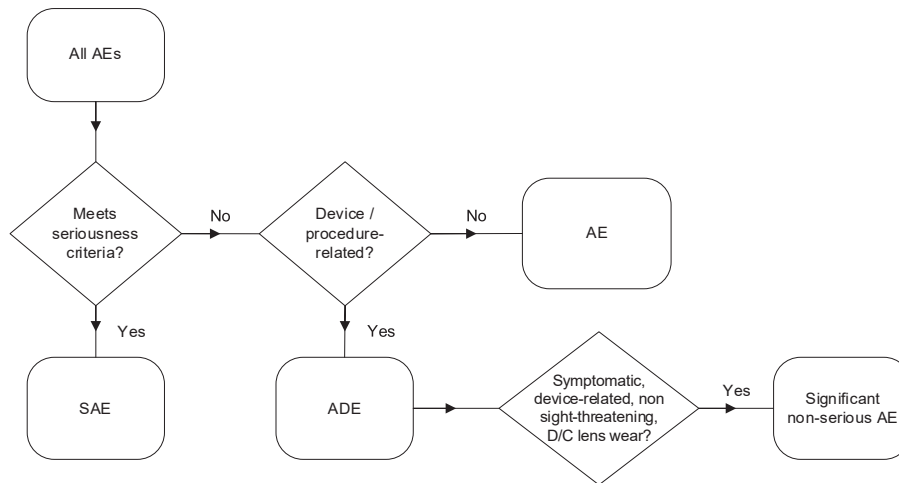
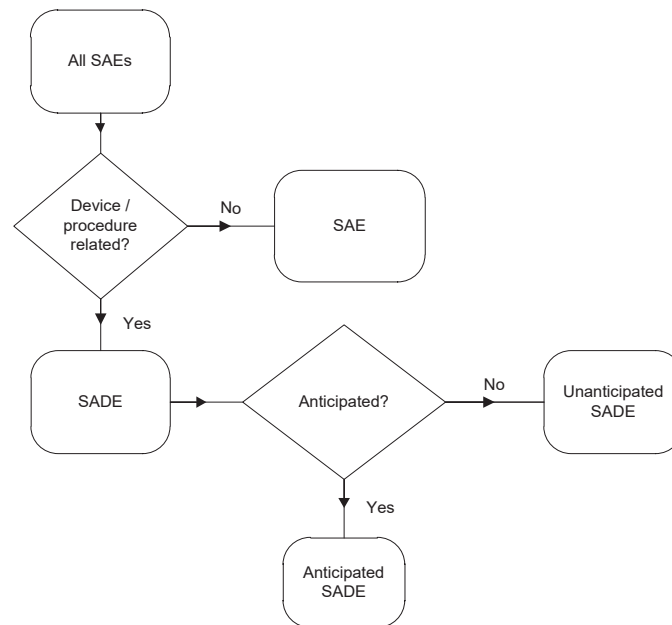


Figure 11-2 Categorization of All Serious Adverse Events



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:
 - o Central or paracentral location

- o Penetration of Bowman's membrane
 - o Infiltrates > 2 mm diameter
 - o Iritis
 - o Increase in intraocular pressure
 - o Culture positive for microorganisms
 - o 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 BCVA from baseline visit that fails to resolve
- Uveitis (anterior, intermediate, or posterior)
- Corneal abrasion affecting $\geq 50\%$ of corneal surface area

Note: For cultured events, document available results in the narrative section(s) of the corresponding ADE-SAE eCRF.

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 occurrences 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 BCVA from baseline 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 and Contact Lens Care Products.

Device Deficiencies

A device deficiency is an 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 *any protocol-specific parameters* [REDACTED] evaluated during the study are to be reviewed by the investigator. Any untoward (unfavorable and unintended) change in a *protocol-specific 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 signing of informed consent. Any preexisting 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.

In addition, temporary lens awareness or visual changes during the fitting process are not considered AEs if the investigator assesses that the symptom(s) can reasonably resolve within the anticipated adaptation period.

For each recorded event, the ADE/SAE documentation must include: the 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.
A printed copy of the completed serious adverse event and adverse device effect and/or device deficiency eCRF must be included with product returns, if applicable.
- 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.

In addition to recording all AEs into the EDC system, any AEs and device deficiencies for nonstudy marketed devices/products (i.e., CLEAR CARE® Cleaning & Disinfecting Solution used concomitantly during the study 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.

Note, 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 are upgraded from nonserious to serious or from unrelated to related.

11.4 Return Product Analysis

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).

11.5 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study. [REDACTED] If the treatment assignment needs to be unmasked 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 treatment may be unmasked prior to contact with the study sponsor. The study sponsor must be informed of all cases in which the masking 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 3 months after subject has 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 who are pregnant (as stated by the subject) at the time of study entry are excluded from participation. However, pregnancy should be included in the corresponding eCRF if a woman becomes pregnant (as stated by the subject) 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. Subjects who become pregnant during the study will not be discontinued; however, data will be excluded from the effectiveness analysis because pregnancy can alter refraction and VA results.

12 ANALYSIS PLAN

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum, as well as confidence intervals (CIs) or confidence limits (CLs) where applicable. Categorical variables will be summarized with frequencies and percentages from each category.

Any deviations to the 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.

[REDACTED]

12.1 Subject Evaluability

Final subject evaluability must be determined prior to breaking the code for masked treatment assignment and locking the database, based upon the data evaluability plan (DEP).

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]

[REDACTED], 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 study 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].

12.2.3 Per Protocol Analysis set

The per protocol (PP) analysis set is a subset of FAS and excludes all data/subjects that have met any of the critical deviation or evaluability criteria identified in the DEP.

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 primary effectiveness endpoint, [REDACTED]

[REDACTED]

[REDACTED] evaluations will use the FAS as the primary analysis set. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

All effectiveness analyses will be carried based on the randomization assignment.

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to demonstrate NI in VA at distance when wearing T30 MFfA lenses compared to ULTRA MFfA lenses, after 30 days of wear (Day 30).

The primary endpoint is binocular HC/HI VA at distance (4 m) at Day 30 with study lenses, collected on the logMAR scale.

12.4.1.1 Statistical Hypotheses

The null and alternative hypotheses are formulated in terms of the predefined margin of 0.05 for NI:

$$H_0: \mu_{(T)} - \mu_{(C)} \geq 0.05$$

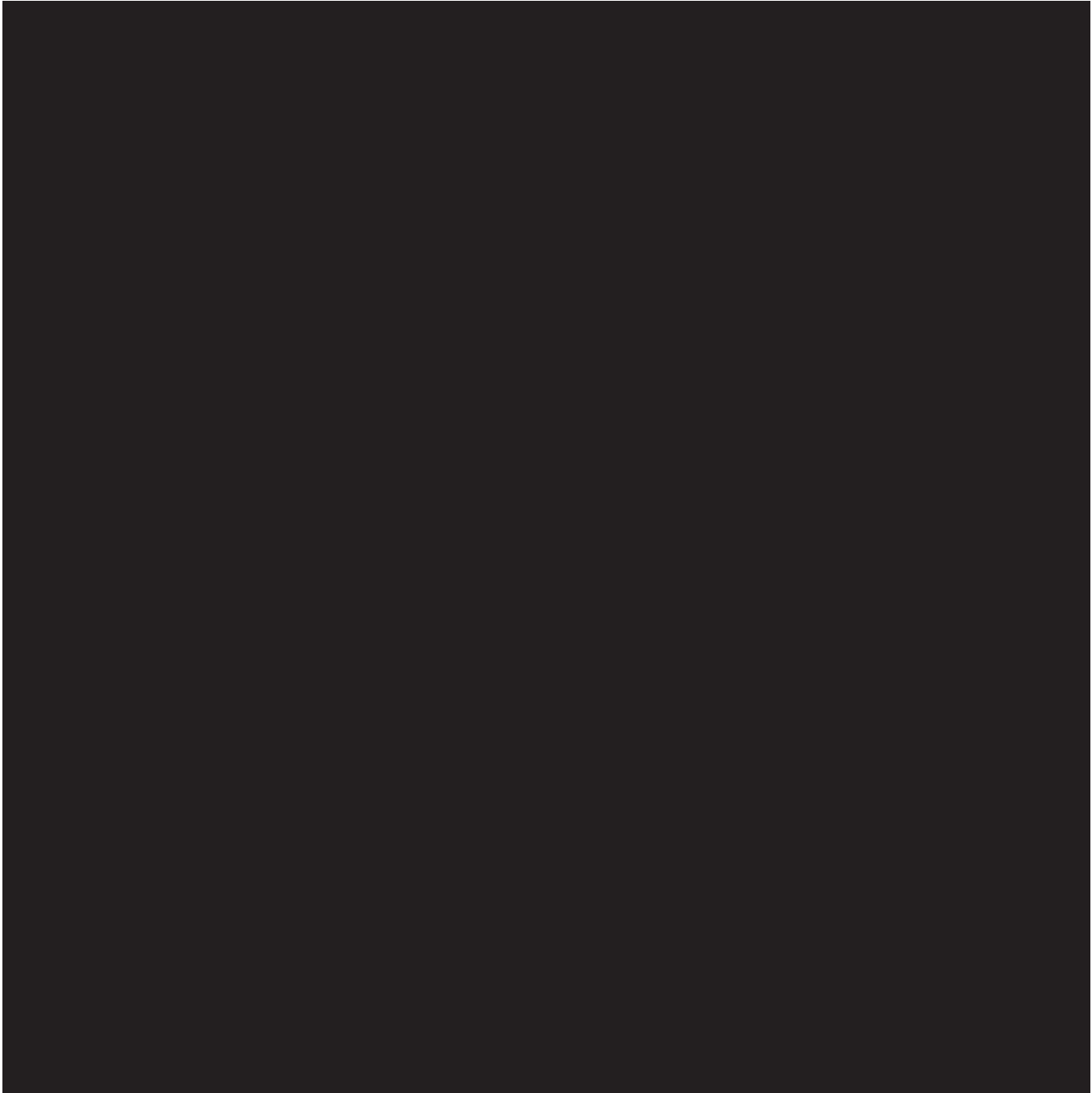
$$H_a: \mu_{(T)} - \mu_{(C)} < 0.05$$

where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance binocular HC/HI VA at Day 30 for T30 MFfA and ULTRA MFfA, respectively, in logMAR scale.

12.4.1.2 Analysis Methods

A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, visit, lens-by-visit interaction, period, and study lens sequence. Within-subject correlation due to crossover will also be accounted for in the model.

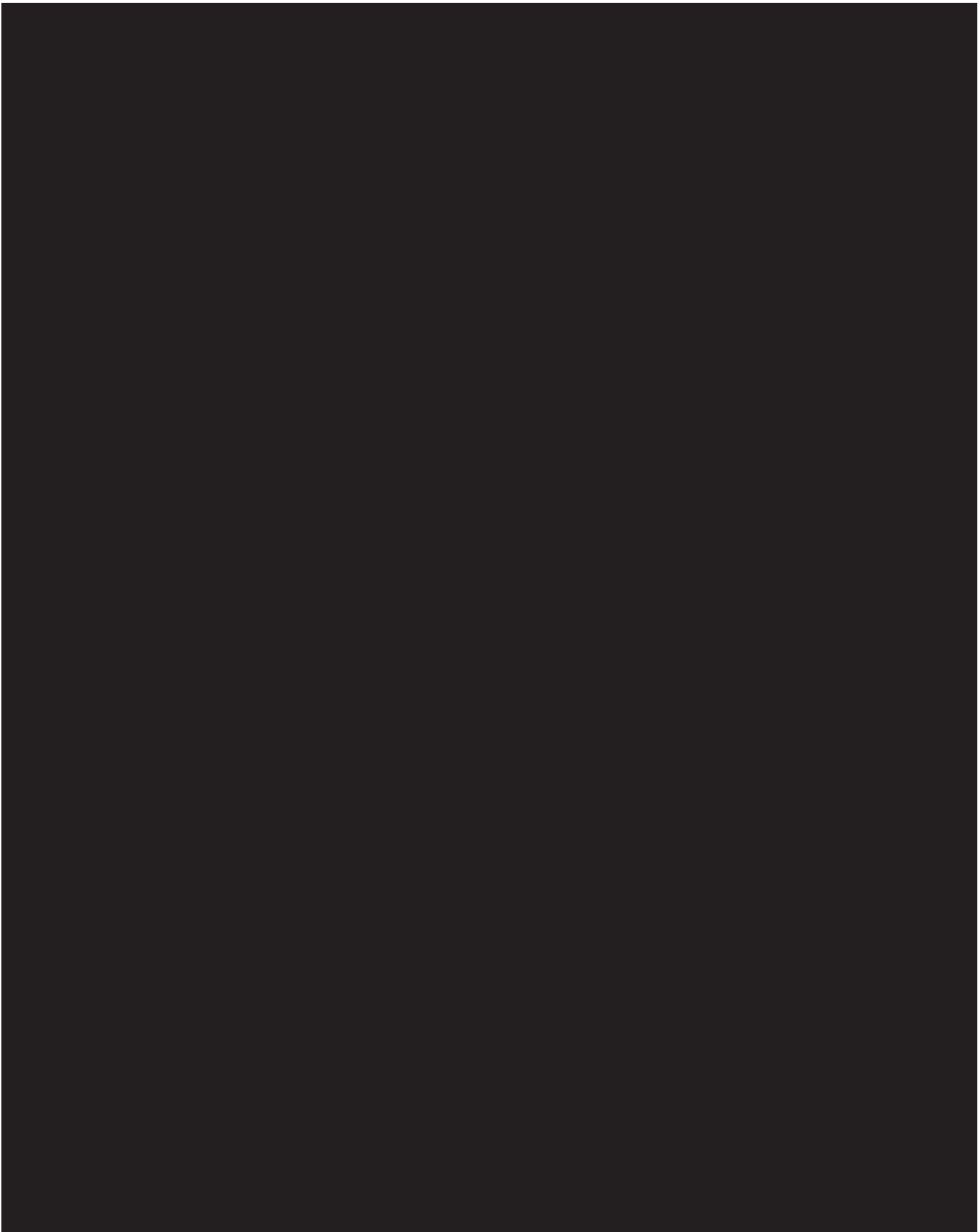
Lens difference (T30 MFfA minus ULTRA MFfA) and the corresponding one-sided 95% upper confidence limit (UCL) at Day 30 will be computed. Noninferiority will be declared if the UCL is less than 0.05.

















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 effectiveness 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, frequencies 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 ≥ 2 grades 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.



12.8 Interim Analyses and Reporting

There are no plans to conduct an interim analysis and no criteria by which the study would be terminated early based upon statistical determination.

12.9 Sample Size Justification

Sample size calculation is based on a prior feasibility clinical study ([REDACTED]

[REDACTED]

[REDACTED]

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. For this study, the principal investigator and subinvestigators must be eye care professionals appropriately trained and licensed to diagnose and treat subjects with the condition under study.

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 GCPs; international and national regulations, laws, and guidelines; EN ISO 14155; 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. The investigator is not allowed to deviate from the protocol except to protect the rights, safety, and well-being of human subjects under emergency

circumstances. Emergency deviations may proceed without prior approval of the sponsor and the IRB/IEC, but shall be documented and reported to the sponsor and the IRB/IEC as soon as possible. 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. Failure to implement identified corrective and preventative actions may result in site closure by the sponsor. 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 IB, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. Any additional requirements imposed by the EC or regulatory authority shall be followed. 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 investigator must have a defined process in case a subject would like to withdraw their consent(s). The investigator is the designated contact point for any such withdrawals.

The investigator must have a defined process in case a subject would like to exercise any of their rights under applicable data protection laws. The investigator is the designated contact point for any such requests.

The study sponsor assures that the key designs of this protocol will be registered on public databases where required by current regulations, and, as applicable, results will be posted.

15 REFERENCES

15.1 Regulations and Standards

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

- ISO 11980 Ophthalmic optics - Contact lenses and contact lens care products - Guidance for clinical investigations
- EN ISO 14155 - Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- 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.



