Alcon

Device Protocol for CLE383-P006 / NCT05138783

Title: Clinical Performance of Two Daily Disposable Soft Contact Lenses

Protocol Number:	CLE383-P006
Clinical Investigation Type:	Postmarket Interventional / Confirmatory
Test Product:	PRECISION1™ (verofilcon A) spherical 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 package inserts, 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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1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as PRECISION1 (or PRECISION1 soft contact lenses)
Name of Comparator Product(s)	Throughout this document, test product(s) will be referred to as Biotrue (or Biotrue® ONEday soft contact lenses)
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.*
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) or comparator and whether anticipated or unanticipated. *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 or comparator product.* Requirements for reporting Adverse Events in the study can be found in Section 11.

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 related to the investigational medical device or the comparator.* 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 Package Insert.

Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Postmarketing / Postauthorization study	Any study conducted within the conditions laid down in product labelling and other conditions laid down for the marketing of the product or under normal conditions of use. A postmarketing study falls either within the definitions of an interventional or a noninterventional study and may also fall within the definition of a postapproval study.
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)	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 preexisting 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.*
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.
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
BCVA	Best corrected visual acuity
Biotrue	Biotrue ONEday soft contact lenses
CFR	Code of Federal Regulations
CI	Confidence interval
CIP	Clinical investigation plan
COL	Clinical operations lead
CRF	Case report form
CSM	Clinical site manager
CTT	Clinical trial team
D	Diopter
DEP	Deviations and evaluability plan
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
GCP	Good Clinical Practice
ICF	Informed consent form
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
[redacted]	[redacted]
LogMAR	Logarithm of the minimum angle of resolution
[redacted]	[redacted]
MOP	Manual of procedures
N	Number of subjects
N/A	Not applicable
NI	Noninferiority
OD	Right eye
OS	Left eye
PP	Per protocol
PRECISION1	PRECISION1 soft contact lenses
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SLE	Slit lamp examination
SOP	Standard operating procedure
[redacted]	[redacted]
US	United States
VA	Visual acuity

Abbreviation	Definition
[redacted]	[redacted]

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional
Investigational products	Test Product: PRECISION1 soft contact lenses (PRECISION1) [redacted] Comparator Product: Biotrue ONEday soft contact lenses (Biotrue) [redacted]
Purpose and Scientific Rationale for the Study	To compare the clinical performance of PRECISION1 contact lenses with Biotrue contact lenses using visual acuity (VA) [redacted]
Objective(s)	The primary objective of this study is to demonstrate noninferiority in visual acuity at distance when wearing PRECISION1 contact lenses compared to Biotrue contact lenses. [redacted]. The safety objective of this study is to describe the safety profile of the study products.
Endpoint(s)	Primary Effectiveness • Distance VA (OD, OS; logMAR) with study lenses [redacted] ▪ [redacted] ▪ [redacted] ▪ [redacted]

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

	[redacted] Safety • Adverse events • Biomicroscopy findings • Device deficiencies
Study Design	This is a prospective, randomized, controlled, double-masked, bilateral crossover, daily wear, multicenter clinical study. Subjects will be expected to attend 3 visits. The total duration of a subject's participation in the study will be up to 22 days. Subjects will be expected to wear their study contact lenses daily [redacted] for at least 10 hours per day. The day prior to Visit 2 and the day prior to Visit 3, subjects will be expected to wear the study lenses for at least 16 hours. [redacted]

Subject population	Volunteer subjects aged 18 or over who are habitual spherical soft contact lens wearers (excluding current/previous PRECISION1, Biotrue and DAILIES TOTAL1® habitual 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. [redacted] Planned number of subjects enrolled/consented: ~128 Planned number of completed subjects: 116
Sites and Locations	Planned number of clinical sites: ~ 8 Planned locations: US
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	• Successful wearers of spherical soft contact lenses with at least 3 months wearing experience, with a minimum wearing time of 5 days per week and 10 hours per day. • Able to wear contact lenses within a range of sphere power from -1.00 to -6.00 D (0.25 D steps) and subject must possess spectacles and willing to wear habitual spectacles for vision correction when study lenses are not worn, as needed. • Willing to wear contact lenses for at least 16 hours on the day prior to Visit 2 and Visit 3.
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Participation of the subject in a clinical trial within the previous 30 days or currently enrolled in any clinical trial. • Habitual PRECISION1, Biotrue, and DAILIES TOTAL1 contact lens wearers. • Any monovision and multifocal lens wearers. • [redacted]
Data analysis and sample size justification	**Planned Data Analysis** To address the primary [redacted] objective, planned analyses are summarized below:

Endpoint	Comparison	Statistical Method
Primary		
Distance VA	PRECISION1 vs Biotrue Noninferiority	Mixed effects repeated measures NI margin = 0.05 (logMAR)

[redacted]

[redacted]

	[redacted]
Associated materials	Lubrication/rewetting drops will not be permitted.

Table 3–1 Schedule of Study Procedures and Assessments

Procedure / Assessment	**Prescreening (optional)**	**Visit 1** Screening / Baseline / Dispense Lens 1 [redacted]	**Visit 2** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 3** Week 1 Follow-up Lens 2 / Exit	**Early Exit**	**Unscheduled Visit**
		[redacted]	8 (-0/+3) days after Visit 1 [redacted]	8 (-0/+3) days after Visit 2	**N/A**	**N/A**
Informed Consent		✓				
Demographics		✓				
Medical History‡‡		✓	✓	✓	✓	✓
Concomitant Medications‡‡		✓	✓	✓	✓	✓
Inclusion/Exclusion		✓				
Habitual lens information (brand, power, lens solution)		✓				
VA with habitual correction (OD, OS, logMAR distance) *		✓		✓ (Exit procedure)	✓	(✓)
Manifest refraction (OD, OS, logMAR distance) *		✓	(✓)	(✓)	(✓)	(✓)
BCVA with manifest refraction (OD, OS, logMAR distance)		✓	(✓)	(✓)	(✓)	(✓)
Biomicroscopy		✓	✓	✓	✓	✓
[redacted]	[redacted]	[redacted]				
Trial lens fitting (Test and Comparator) & assessments: *		✓				

Procedure / Assessment	**Prescreening (optional)**	**Visit 1** Screening / Baseline / Dispense Lens 1 [redacted]	**Visit 2** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 3** Week 1 Follow-up Lens 2 / Exit	**Early Exit**	**Unscheduled Visit**
		[redacted]	8 (-0/+3) days after Visit 1 [redacted]	8 (-0/+3) days after Visit 2	**N/A**	**N/A**
• VA (logMAR distance) [redacted]						
Randomize✧		✓				
Dispense (provide) study lenses *		✓	✓			(✓)
VA (logMAR distance) with study lenses, (OD, OS)			✓	✓	(✓)	(✓)
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]

Procedure / Assessment	**Prescreening (optional)**	**Visit 1** Screening / Baseline / Dispense Lens 1 [redacted]	**Visit 2** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 3** Week 1 Follow-up Lens 2 / Exit	**Early Exit**	**Unscheduled Visit**
		[redacted]	8 (-0/+3) days after Visit 1 [redacted]	8 (-0/+3) days after Visit 2	**N/A**	**N/A**
[redacted]						
AEs		✓	✓	✓	✓	✓
Device Deficiencies ~		✓	✓	✓	✓	✓
Exit Form		(✓)	(✓)	✓	✓	(✓)

(✓) Assessment performed as necessary, e.g., decrease of VA by 2 lines or more with investigational product (IP) compared to BCVA with manifest refraction at Visit 1

[redacted]

✧ Randomization should occur at Visit 1 unless communicated otherwise by the sponsor.

‡ All ocular and targeted systemic meds / medical history

[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.

[redacted]

5 INTRODUCTION

5.1 Rationale and Background

It is estimated that soft contact lenses account for over 90% of lens fits. Furthermore, it was reported that almost 32% of soft contact lenses were prescribed in a daily disposable modality. PRECISION1 is a new daily disposable silicone hydrogel contact lens with a material that combines high oxygen transmissibility with a low modulus of elasticity. PRECISION1 contact lenses are intended for the optical correction of refractive ametropia in persons with nondiseased eyes requiring subjects to wear spectacles for vision correction. The unique properties of PRECISION1 contact lenses provide precise vision, long lasting comfort, and excellent handling.

5.2 Purpose of the Study

The purpose of this study is to evaluate the overall clinical performance of PRECISION1 contact lenses when compared to another commercially available daily disposable contact lens, Biotrue ONEday.

The endpoints for this study were selected to fulfill the primary [redacted] objective[redacted] of the study. [redacted]. [redacted]. Biotrue contact lenses were chosen as the comparator product because these lenses have the same wear modality.

[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 package insert and are managed through review of safety assessments outlined in this protocol.

Contact lenses may offer improved peripheral vision and the convenience of not wearing spectacles. Material properties and design characteristics of the test contact lens are features consistent with successful contact lens wear.

PRECISION1 and Biotrue contact lenses are for daily wear use under a daily disposable wear modality; further details on any known potential risks and benefits can be found in the package insert.

PRECISION1 and Biotrue contact lenses are not intended for use with a cleaning/disinfecting solution, and the biocompatibility with lens care solutions and any associated clinical effects are unknown.

A summary of the known potential risks and benefits associated with PRECISION1 can be found in the package insert. Risks are minimized by compliance with the eligibility criteria and study procedures, and through close supervision by a licensed clinician during exposure to the study lenses.

The site personnel will educate subjects on proper hygiene and lens handling, and compliance with the use of contact lenses according to the protocol. Subjects should be instructed not to wear contact lenses while sleeping or swimming. The site personnel will also advise the subjects to remove contact lenses and return for prompt follow-up of symptoms, such as ocular discomfort, foreign body sensation, excessive tearing, vision changes, or hyperemia.

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

There may also be unknown risks to use of the comparator. 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 package insert for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
To demonstrate noninferiority in visual acuity at distance when wearing PRECISION1 contact lenses compared to Biotrue contact lenses.	Distance VA (OD, OS; logMAR) with study lenses

6.2 Secondary Objective(s)

Not Applicable.

[redacted]

[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

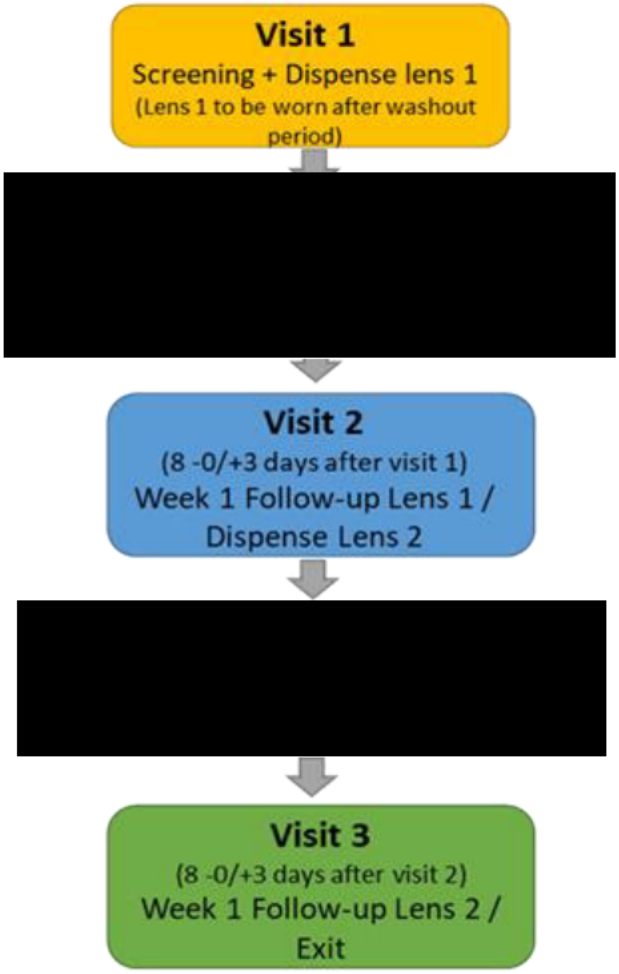
7.1 Study Design

This is a prospective, randomized, controlled, double-masked bilateral crossover, daily wear, multicenter clinical study. Habitual soft contact lens wearers will be randomized in 1 of the 2 crossover sequences. Subjects and investigators will be masked. [redacted]

Subjects will be expected to attend 3 visits: Screening/Baseline/Dispense Lens 1, Visit 2 (Week 1 Follow-up Lens 1/Dispense Lens 2), and Visit 3 (Week 1 Follow-up Lens 2/Exit). The total duration of a subject's participation in the study will be up to 22 days. Subjects will be expected to wear their study contact lenses daily for at least 10 hours per day.

On the day prior to Visit 2 and the day prior to Visit 3, subjects will be instructed to wear the study lenses at least 16 hours. [redacted]pectacles or no lens wear) of at least 12 hours will be required after Visit 1 and after Visit 2.

Figure 7-1 **Study Visit Schedule Outline**



7.2 Rationale for Study Design

[redacted]

The crossover design will ensure that the same subject is exposed to both the test and comparator lens materials; therefore, both objective assessments and subjective responses will be obtained for both lenses from the same subject. The study will include only those subjects who are current wearers of spherical soft contact lenses in both eyes with at least 3 months wearing experience, with a minimum wearing time of 5 days per week and 10 hours per day. This will avoid confounding subjective and safety responses in nonadapted subjects. Furthermore, the subjects will not be permitted to use lubrication/rewetting drops during the duration of the study [redacted] The study will exclude any habitual PRECISION1, Biotrue and DAILIES TOTAL1 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 wish to wear their contact lenses in monovision modality during the study and multifocal lens wearers.

[redacted]

7.3 Rationale for Duration of Treatment/Follow-Up

Subjects will wear each study product bilaterally for approximately 1 week. [redacted] The primary [redacted] endpoint will be assessed on approximately after 1 week of wearing each study product. [redacted]

The duration of use of each study product is in accordance with the respective product labeling (see package inserts).

7.4 Rationale for Choice of Comparator Product

Biotrue contact lenses were chosen as the comparator product because these lenses have the same wear modality and replacement schedule.

7.5 Data Monitoring Committee

Not Applicable.

8 STUDY POPULATION

The study population consists of male and female subjects (aged 18 or over who are wearers of spherical soft contact lenses in both eyes with at least 3 months of wearing experience, with a minimum wearing time of 5 days per week and 10 hours per day. Subjects who are current or previous PRECISION1, Biotrue ONEday, and DAILIES TOTAL1 habitual lens wearers will be excluded. [redacted] It is aimed to enroll (consent) approximately 128 subjects in approximately 8 sites in the US, with a target of 116 total subjects treated, with 12 (intended minimum) to 20 (intended maximum) subjects per site. Additional subjects may be enrolled at specific sites with prior sponsor approval. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 3 weeks; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol. Because a 10% screening failure rate is expected, approximately 128 subjects are expected to be enrolled.

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. Willing and able to attend all scheduled study visits as required per protocol.
3. Subject must be at least 18 years of age.
4. Successful wear of spherical soft contact lenses in both eyes for a minimum of 5 days per week and 10 hours per day during the past 3 months.

[redacted]

[redacted]

[redacted]

8. Subject must be willing to wear contact lenses for at least 16 hours of lens per day on the day prior to Visit 2 and the day prior to Visit 3.

9. 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. Habitual lens wearers within the past 6 months of PRECISION1, Biotrue, and DAILIES TOTAL1 and any monovision & multifocal lens wearers.

[redacted]

[redacted]

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

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):	PRECISION1 soft contact lenses [redacted]
Comparator Product(s) (If applicable):	Biotrue ONEday soft contact lenses [redacted]

Table 9–1 Test Product

Test Product	PRECISION1 soft contact lenses (PRECISION1)
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway

	Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	Precision1 (verofilcon A) spherical soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with nondiseased eyes with up to approximately 1.50 diopters (D) of astigmatism that does not interfere with visual acuity. The lenses are to be prescribed for single use, daily disposable wear. The lenses are not intended to be cleaned or disinfected and should be discarded after a single use.
Product description and parameters available for this study	• Material: verofilcon A • Water content: 51% • Power range: -1.00 to -6.00 D, 0.25 D steps • Base curve (mm): 8.3 • Diameter (mm): 14.2
Formulation	Please refer to package insert.
Usage	• Wear: o Daily Wear o Bilateral • Replacement period: Daily Disposable • Exposure: o 16 days total duration (test and comparator) ▪ Test Product: 8 (-0/+3) days ▪ Comparator Product: 8 (-0/+3) days • Lens Care: N/A
Number/Amount of product to be provided to the subject	Subjects will be dispensed study lenses at Visit 1 and Visit 2. No spare lenses will be provided to the subject.

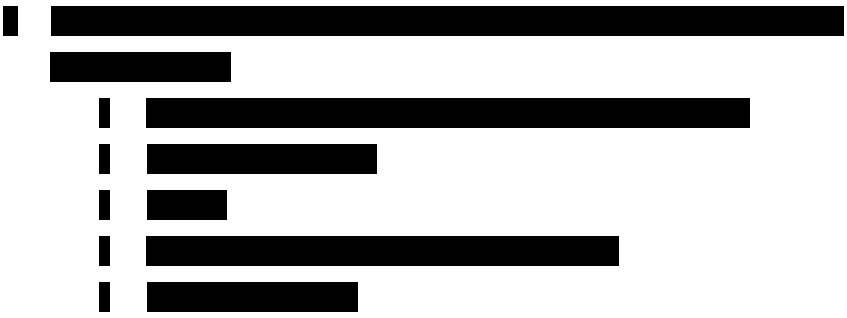
Packaging description	Blister foil pack
Labeling description	• Lens Foil label includes: - lens identifier - base curve - diameter - packing solution - power - lot number - expiration date - content statement - investigational device statement - sponsor information - country of origin 
Storage conditions	Stored at room temperature.
[redacted]	[redacted].
Supply	Alcon will provide a fitting set and study lenses. Refer to the MOP for a detailed description

Table 9–2 Comparator Product

Comparator Product(s)	Biotrue ONEday soft contact lenses (Biotrue)
Manufacturer	Bausch & Lomb Incorporated 1400 North Goodman Street

	Rochester, New York 14609 USA
Indication for Use	The Bausch + Lomb Biotrue ONEday (nesofilcon A) Soft (Hydrophilic) Contact Lens is indicated for the daily wear correction of refractive ametropia (myopia, hyperopia and astigmatism) in aphakic and/or nonaphakic persons with nondiseased eyes, exhibiting astigmatism of 2.00 diopters or less, that does not interfere with visual acuity.
Product description and parameters available for this study	• Material: nesofilcon A • Water content: 78% • Power range: -1.00 to -6.00 D in 0.25 D steps • Base curve (mm): 8.6 • Diameter (mm): 14.2
Formulation	Please refer to package insert.
Usage	• Wear: o Daily Wear o Bilateral • Replacement period: Daily Disposable • Exposure: o 16 days total duration (test and comparator) ▪ Test Product: 8 (-0/+3) days ▪ Comparator Product: 8 (-0/+3) days • Lens Care: N/A
Number/Amount of Product to be Provided to the subject	Subjects will be dispensed study lenses at Visit 1 and Visit 2. No spare lenses will be provided to the subject.
Packaging description	Blister foil pack

Labeling description	• Lens Foil label includes: - lens identifier - base curve - diameter - packing solution - power - lot number - expiration date - content statement - investigational device statement - sponsor information - country of origin • [redacted]
Storage conditions	Stored at room temperature.
[redacted]	[redacted]
Supply	Alcon will provide a fitting set and study lenses. Refer to the MOP for a detailed description.

More information on the test and comparator products can be found in the respective Package Inserts.

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: Test product then Comparator product or Comparator product then Test product, respectively.

Sequence	EDC/randomization integration system	Lens Name
Sequence 1	[redacted]	PRECISION1/Biotrue
Sequence 2	[redacted]	Biotrue/PRECISION1

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

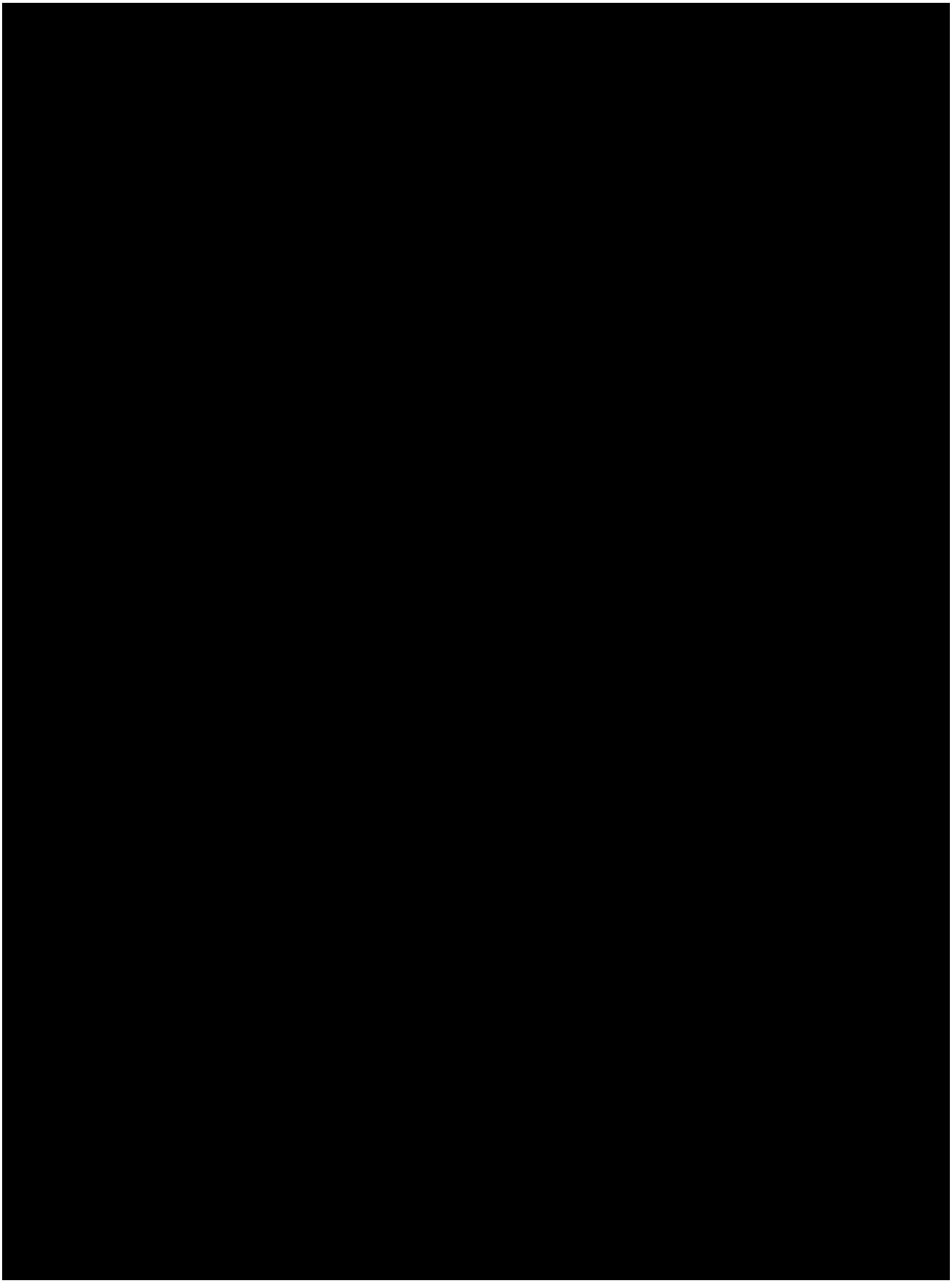
A randomization list will be generated using a validated system that automates the random assignment of treatments (lens sequence) to randomization numbers in the specified ratio. Subjects will be assigned treatment (lens sequence) according to the randomization list uploaded in the randomization system. 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 treatment arms. 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) assignment to be dispensed to the subject.

9.4 Treatment masking

This study is double-masked, with subjects randomized to use PRECISION1 contact lenses or Biotrue contact lenses for the duration of a 1-week treatment period per lens type. [redacted]

[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. During the study, the masked investigator must designate study staff to 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

Subjects will be expected to attend 3 office visits, as shown below.

Visit #	**Visit Type**	**Visit Window**
Visit 1	Screening/Baseline/Dispense Lens 1	N/A
Visit 2	Week 1 Follow-up Lens 1/Dispense Lens 2	8 (-0/+3) days after Visit 1
Visit 3	Week 1 Follow-up Lens 2/Exit	8 (-0/+3) days after Visit 2

Unscheduled Visits and Early Exit Visits are allowed, if necessary.

Study lenses will be provided to the subjects to take home for daily wear during the course of the trial.

Study randomization will occur at Visit 1 with assigned lenses provided to take home at Visit 1 and Visit 2. Study contact lens fitting will occur at Visit 1 for both study lenses. If a subject cannot be successfully fit (either study lens) according to the study lens fitting guides as determined by the investigator, they will be required to exit from the study.

Lubrication/rewetting drops will not be permitted during this study.

Study tests, procedures, and questionnaires will be conducted as outlined in the MOP.

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.

[redacted]

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 in the subject source documents. See Section 11 for further details regarding AE collection and reporting. Note: AEs must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or randomized).

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. Device deficiencies on comparator lenses should be reported per the manufacture's guidelines. Note: Device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or randomized).

[redacted]

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
- Record changes in medical condition or concomitant medication
- Collect device deficiency information
- Biomicroscopy

The investigator may perform additional procedures for proper diagnosis and treatment of the subject according to Table 3-1 or at their discretion. 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, 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 study product assignment and dispensing 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 re-used.

10.4.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the investigator after signing the 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 and the MOP for details.

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 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.

10.5.1 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

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 AEs

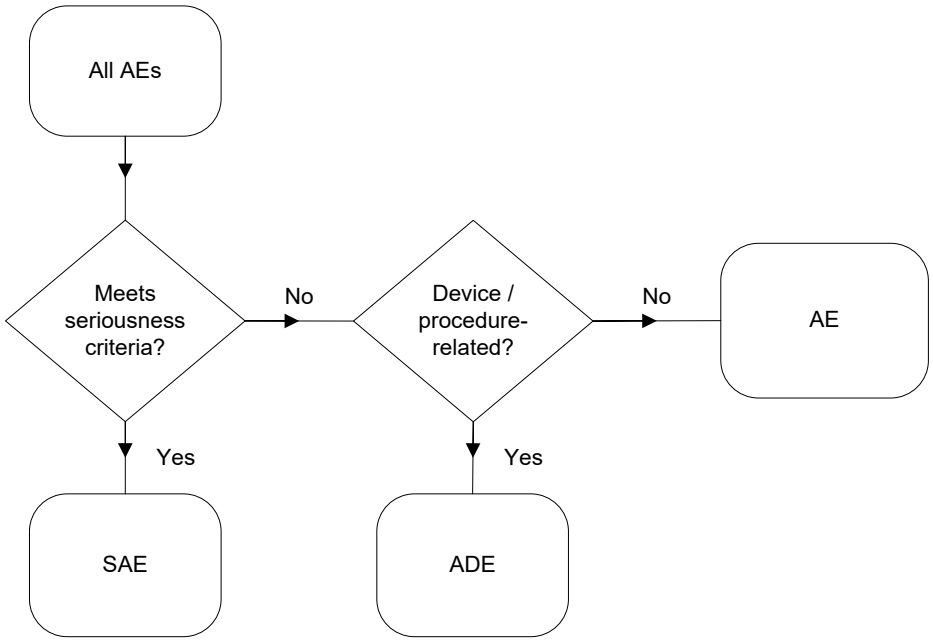
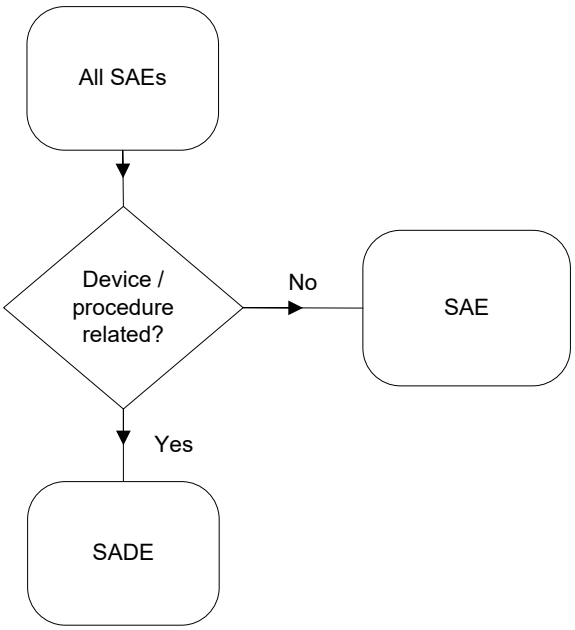


Figure 11-2 Categorization of All Serious Adverse Events



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:

- Len missing/folded/fragments/Lens cloudy/dirty
- Lens surface/edge defect
- Torn lens during handling/in pack
- Packaging deficit (e.g., blister strip damage, primary/secondary label mismatch, mislabeled product, tampered seal)
- Potential contaminant

11.1 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 since your last study visit?"

Additionally, 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.

11.2 Procedures for Recording and Reporting

AEs are collected from the time 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 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

- All SAEs must be reported immediately (within 24 hours) of the investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and Device deficiencies must be reported within 10 calendar days 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.

- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- 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 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.

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 upon 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.

11.3 Return product analysis (as applicable)

Alcon 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. These products should be returned to the sponsor at the end of the study, unless instructed otherwise by the sponsor.

11.4 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study. In the event of a medical emergency where the knowledge of subject treatment is required, individual investigator(s) will have the ability to unmask the treatment assignment for a specific subject. If time allows, the appropriate study sponsor representative should be contacted prior to unmasking. 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.

11.5 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 subject exit from study, 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 discontinuation or exit must be documented and available upon the study sponsor's request. All complaints received after this time period will be considered and processed as spontaneous 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.

11.6 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 Pregnancy eCRF form in EDC 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 (SD), median, minimum, and maximum, as well as confidence intervals (CIs) or confidence limits 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.

12.1 Subject Evaluability

Final subject evaluability must be determined prior to breaking the code for masked treatment (lens sequence) assignment and locking the database, based upon the Deviations and 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] 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 [redacted] evaluated in this study.

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, [redacted] effectiveness endpoint [redacted] effectiveness evaluation will use the FAS as the primary analysis set. [redacted]

[redacted]

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to demonstrate noninferiority in visual acuity at distance when wearing PRECISION1 contact lenses compared to Biotrue contact lenses. The primary endpoint is distance VA with study lenses, collected for each eye in logMAR.

12.4.1.1 Statistical Hypotheses

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

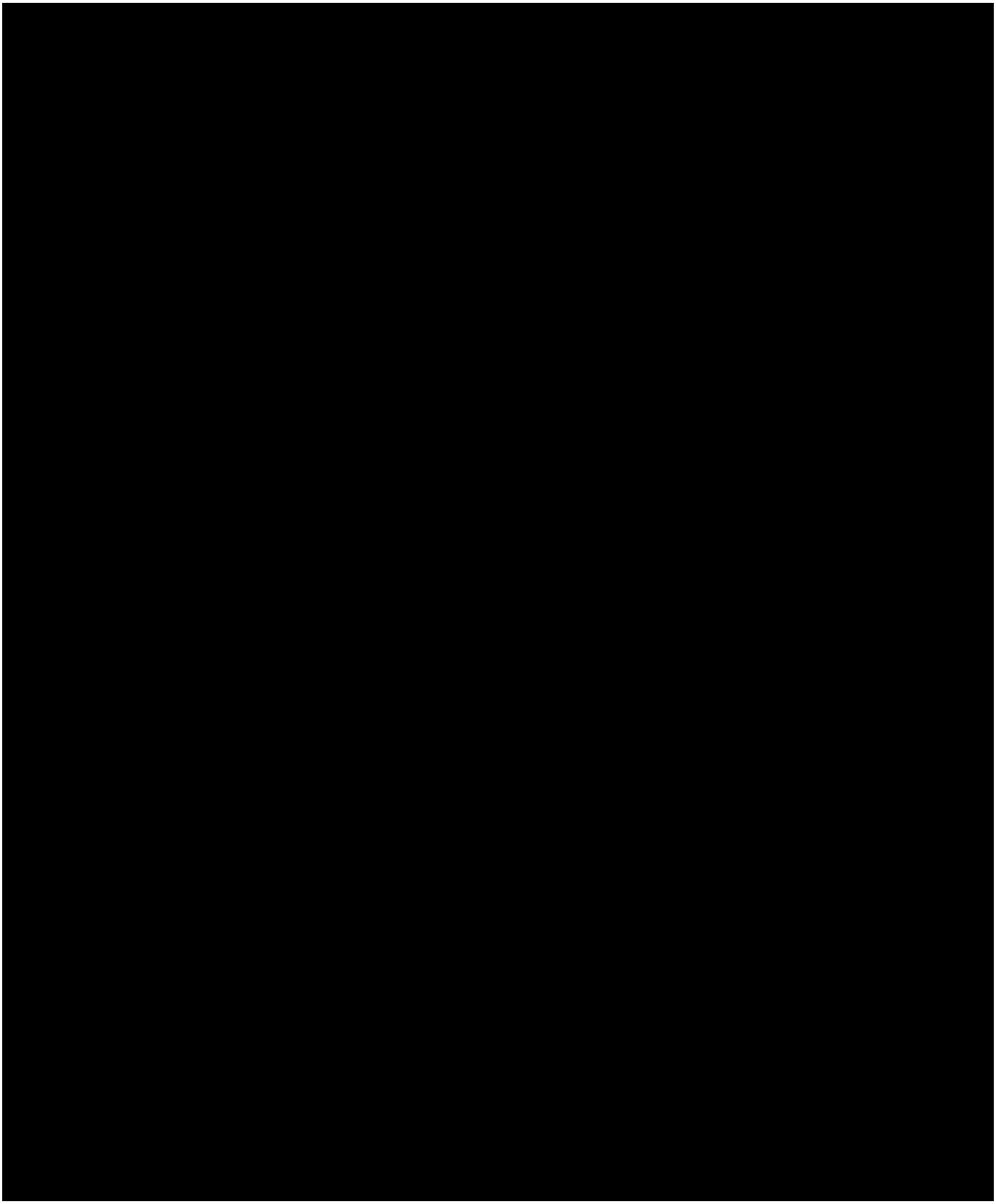
$$H_0: \mu_{(T)} - \mu_{(C)} \geq 0.05$$
$$H_a: \mu_{(T)} - \mu_{(C)} < 0.05$$

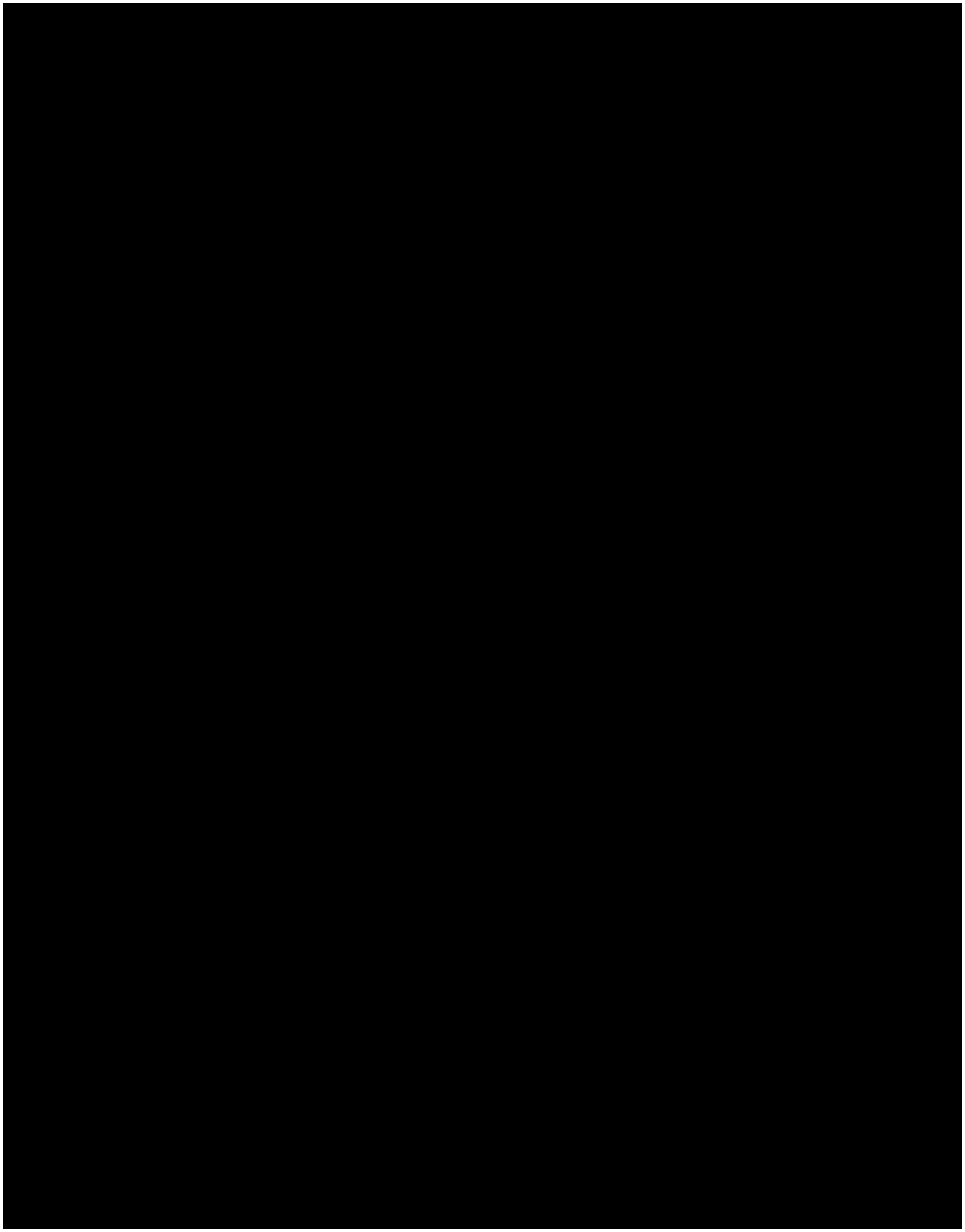
where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance VA for PRECISION1 and Biotrue, respectively, on the logMAR scale.

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, period, and sequence. Within-subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference (PRECISION1 minus Biotrue) and the corresponding one-sided 95% upper confidence limit will be computed. Noninferiority in distance VA will be declared if upper confidence limit is less than 0.05.

[redacted]





[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 [redacted]

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 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, as well as for AEs that occur between treatment periods.

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.

[redacted]

12.8 Sample Size Justification

[redacted]

Primary Effectiveness

To demonstrate noninferiority (margin = 0.05 in logMAR; ½ line in Snellen) in distance VA as a one-tailed hypothesis with α=0.05, and using a standard deviation of 0.0462 for paired differences, 80% power can be attained with a sample size of 8 (4 per sequence).

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.

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