Alcon

Device Protocol for CLA306-P001 / NCT04908488
Title: Clinical Performance of Two Daily Disposable Toric Soft Contact Lenses

Protocol Number:	CLA306-P001
Development Stage of Project:	Product Support
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	PRECISION1™ for Astigmatism contact lenses (verofilcon A)

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 Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, all applicable regulatory authority regulations, and conditions of approval imposed by the reviewing IRB or regulatory authority.
- 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(s) will be referred to as PRECISION1 for Astigmatism or P1fA.
Name of Control Product(s)	Throughout this document, control product(s) will be referred to as 1-DAY ACUVUE® MOIST for ASTIGMATISM or AMfA.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test product) or control product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test product or control product.*
Adverse Event (AE)	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). *Note: For subjects, this definition includes events related to the test product, the control product, or the procedures involved. For users or other persons, this definition is restricted to events related to the test 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, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.* 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.

Interventional Clinical Trial	A research trial that prospectively assigns, whether randomly or not, human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, and/or a research trial in which diagnostic or monitoring procedures beyond standard of care are conducted and generate outcomes for use in analysis of data.
Investigational Product (IP)	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control 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 a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Product Complaints	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 Subjects	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 that either resulted in: 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. c. inpatient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a preexisting condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* *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, or a congenital abnormality or birth defect. *Refer to Section 11 for additional SAEs.*
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, e.g., human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 LIST OF ACRONYMS AND ABBREVIATIONS

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

Abbreviation	Definition
ADE	Adverse device effect
AMfA	1-DAY ACUVUE MOIST for ASTIGMATISM
AE	Adverse event
BCVA	Best corrected visual acuity
CFR	Code of federal regulations
CI	Confidence interval
CRF	Case report form
COL	Clinical Operations Lead
CSM	Clinical Site Manager
CTT	Clinical Trial Team
D	Diopter
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and drug administration
GCP	Good clinical practice
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
[redacted]	[redacted]
logMAR	Logarithm of the minimum angle of resolution
[redacted]	[redacted]
[redacted]	[redacted]
MOP	Manual of procedures
N/A	Not applicable
NI	Noninferiority
OD	Right eye
OS	Left eye
OU	Both eyes
P1fA	PRECISION1 for Astigmatism
PP	Per protocol
SAE	Serious adverse event
SADE	Serious adverse device effect
SD	Standard deviation
Seq	Sequence
SOP	Standard operating procedure

Abbreviation	Definition
US / USA	United States
UV	Ultraviolet
VA	Visual acuity

3 PROTOCOL SUMMARY

This is a prospective, double-masked, randomized, crossover clinical study. Subjects will be exposed to both test and control lenses to be worn bilaterally in daily disposable wear modality. Group assignment ratio will be 1:1 with a single crossover.

Approximately 8 sites in the USA will enroll approximately 110 subjects. Subjects will be randomized to wear both the test P1fA and the control AMfA. Subjects will be expected to attend 4 visits: (1) Screening/Trial lens fitting and evaluation, (2) Baseline/Dispense Lens 1, (3) Week 1 Follow-up Lens 1/Dispense Lens 2, and (4) Week 1 Follow-up Lens 2/Exit.

Following randomization, study lenses will be ordered for each subject. Lenses will be dispensed and subjects will wear the study lenses in a daily wear, daily disposable modality for up to 11 days.

[redacted]

Investigational product type	Device
Study type	Interventional
Investigational products	Test Product: PRECISION1 for Astigmatism contact lenses (verofilcon A) Control Product: 1-DAY ACUVUE MOIST for ASTIGMATISM (etafilcon A)
Purpose and rationale	To compare the clinical performance of P1fA contact lenses with AMfA contact lenses using subjective endpoints. [redacted]
Objective(s)	The primary objective of this study is to demonstrate noninferiority in the visual acuity (VA) at distance when wearing P1fA contact lenses compared to AMfA contact lenses.

	[redacted]
Endpoint(s)	Primary Effectiveness • Distance VA (logMAR) with study lenses [redacted]

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

	• Medical History/Concomitant Medications Safety • Adverse events • Biomicroscopy findings • Device deficiencies
Study Design	This will be a prospective, randomized, controlled, double-masked, crossover, daily disposable wear clinical study. Subject participation in the study will be approximately 11 days each for two different lenses, totaling approximately 22 days of exposure to study lenses.
Subject population	Volunteer subjects aged 18 or over who are habitual toric soft contact lens wearers (excluding current/previous P1fA and AMfA contact lens habitual 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. Planned number of subjects enrolled/consented: Approximately 110 Planned number of completed subjects: 100
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	• Successful wear of toric soft contact lenses in both eyes for a minimum of 5 days per week and 10 hours per day during the past 3 months. [redacted]
Key exclusion criteria (See Section 8.2 for a	• Current/previous P1fA and AMfA contact lens habitual wearers and any current spherical monovision and multifocal contact lens wearers.

complete list of exclusion criteria)	• 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.
Data analysis and sample size justification	**Planned Data Analysis** To address the primary [redacted] objective[redacted] planned analyses are summarized below:

Endpoint	Comparison	Statistical Model
Primary		
Distance VA	P1fA vs AMfA Noninferiority (NI)	Mixed effect repeated measures NI margin = 0.05 logMAR

[redacted]

	[redacted]
Key words	18 years of age, Daily Disposable Toric Soft Contact Lenses, visual acuity, refractive correction
Associated materials	The use of marketed rewetting drops will not be permitted.

Table 3-1 Schedule of Study Procedures and Assessments

Procedure / Assessment	**Visit 1** Screening / Trial Lens Fitting and Evaluation	**Visit 2** Baseline / Dispense Lens 1	**Visit 3** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 4** Week 1 Follow-up Lens 2 / **Exit**	**Unscheduled Visit**	**Early Exit**
		4 -2/+2 days after Visit 1	8 -0/+3 days after Visit 2	8 -0/+3 days after Visit 3	N/A	N/A
Informed Consent	X	-	-	-	-	-
Demographics	X	-	-	-	-	-
Medical History ∞	X	X	X	X	(X)	X
Concomitant Medications ∞	X	X	X	X	(X)	X
Inclusion / Exclusion	X	-	-	-	-	-
Habitual lens information (brand, power)	X	-	-	-	-	-
VA with habitual contact lens correction (OD, OS, LogMAR distance)*	X	-	-	X	-	X
Keratometry*	X	-	-	-	-	-
Manifest refraction* (OD, OS; sphere, cylinder, axis)	X	-	(X)	(X)	(X)	X
BCVA* (OD, OS logMAR distance with Manifest refraction)	X	-	(X)	(X)	(X)	X
Biomicroscopy	X	X	X	X	(X)	X
Trial lens fitting and evaluation*	X	-	-	-	-	-
Randomize	X	-	-	-	-	-
Order study lenses	X	-	-	-	-	-
Dispense/provide study lenses*	-	X	X	-	(X)	-
Insert study lenses	-	X	X	-	-	-

Procedure / Assessment	**Visit 1** Screening / Trial Lens Fitting and Evaluation	**Visit 2** Baseline / Dispense Lens 1	**Visit 3** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 4** Week 1 Follow-up Lens 2 / **Exit**	**Unscheduled Visit**	**Early Exit**
		4 -2/+2 days after Visit 1	8 -0/+3 days after Visit 2	8 -0/+3 days after Visit 3	**N/A**	**N/A**
[redacted]						
VA (logMAR distance) with study lenses, OD, OS	-	X	X (lens 1 and 2)	X	(X)	X
[redacted]						

Procedure / Assessment	**Visit 1** Screening / Trial Lens Fitting and Evaluation	**Visit 2** Baseline / Dispense Lens 1	**Visit 3** Week 1 Follow-up Lens 1 / Dispense Lens 2	**Visit 4** Week 1 Follow-up Lens 2 / **Exit**	**Unscheduled Visit**	**Early Exit**
		4 -2/+2 days after Visit 1	8 -0/+3 days after Visit 2	8 -0/+3 days after Visit 3	**N/A**	**N/A**
[redacted]						
AEs	X	X	X	X	(X)	X
Device Deficiencies	X	X	X	X	(X)	X
Exit Form	-	-	-	X	-	X

(X) assessment performed as necessary, e.g., decrease of VA by 2 lines or more with investigational product (IP)

* Source only

∞ All ocular and targeted systemic medications/ 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.

5 INTRODUCTION

5.1 Rationale and Background

In this clinical study, the clinical performance of P1fA contact lens will be compared to AMfA contact lens [redacted] The intended use of this contact lens is for vision correction. Therefore, the measurement of distance VA is planned as the primary effectiveness variable. [redacted]

5.2 Purpose of the Study

The purpose of this clinical study is to demonstrate noninferiority in the visual acuity at distance when wearing P1fA contact lenses compared to AMfA contact lenses. [redacted]

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

[redacted]

5.3 Risks and Benefits

The clinical investigation process risks are managed through appropriate training and monitoring according to the protocol-specific monitoring plan. Investigational device risks, including risks associated with use of device and methods and procedures for application of device, are defined in the package insert and/or product labeling 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 P1fA contact lenses are features consistent with successful contact lens wear.

P1fA and AMfA 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.

P1fA and AMfA 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 P1fA contact lenses 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 potential harms associated with on-eye exposure to the new lens materials include toxicity response, blurred vision, and ocular discomfort. In general, when worn for daily disposable wear, the risks with P1fA contact lenses are anticipated to be similar to other marketed soft contact lenses worn for daily disposable wear.

There may also be unknown risks to use P1fA. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight, and monitoring.

Refer to the product label for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6-1 Primary Objective(s)

Objective(s)	Endpoint(s)
Demonstrate noninferiority in VA at distance when wearing P1fA contact lenses compared to AMfA contact lenses.	Distance VA (logMAR) with study lenses

6.2 Secondary Objective(s)

Not applicable.

[redacted]

6.4 Safety Objective(s)

Table 6-3 Safety Objective(s)

Objective(s)	Endpoint(s)
Duty of care and evaluation of safety profile of the investigational products.	AEs Biomicroscopy findings Device deficiencies

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, double-masked, randomized, crossover clinical study. Subjects will be exposed to both test and control lenses to be worn bilaterally in daily disposable wear modality. Group assignment ratio will be 1:1 with a single crossover.

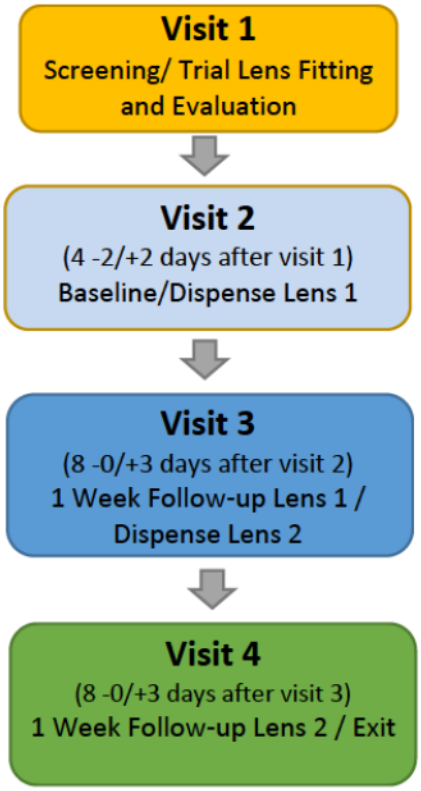
Exposure to study lenses will be 8 days, up to a maximum of 11 days. [redacted]

Subjects will be expected to attend 4 office visits: (1) Screening/Trial lens fitting and evaluation, (2) Baseline/Dispense Lens 1, (3) 1 Week Follow-up Lens 1/Dispense Lens 2, and (4) 1 Week Follow-up Lens2/Exit. The total expected duration of participation in this study is approximately 1 month.

This clinical study will engage approximately 8 clinic sites to enroll approximately 110 subjects with approximately 15-22 subjects per site.

This is a double-masked study design wherein the subjects and the investigator (to the best of the site's ability) will be masked to the details of the study products. Minor differences in lens color, scribe marks, and lens thickness profile between the study lenses could result in potential inadvertent unmasking of the investigator. An unmasked study staff member will prepare the contact lenses for dispensing. All efforts will be taken to keep the investigator masked.

Figure 7-1 **Flowchart of Study Visits**



7.2 Rationale for Study Design

The purpose of this study is to obtain on-eye performance data to compare the clinical performance of P1fA contact lenses with AMfA contact lenses [redacted]

The crossover design will ensure that the same subject is exposed to both the test and control lens materials; [redacted]. The study will include only those subjects who are current wearers of toric 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 as this may confound the primary effectiveness endpoint. The study will exclude any habitual P1fA and AMfA contact lens wearers in order to reduce potential bias of wearers to their habitual contact lenses.

7.3 Rationale for Duration of Treatment/Follow-Up

The duration of product use is in accordance with product labeling.

7.4 Rationale for Choice of Control Product

The AMfA contact lens was chosen as the control product because this lens is a proper device to compare P1fA with regard to VA [redacted] Both the P1fA and AMfA are daily disposable contact lenses that are intended for the optical correction of refractive ametropia (myopia and hyperopia) in phakic and aphakic persons with nondiseased eyes.

7.5 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population consists of male and female subjects (aged 18 or over) with a diagnosis of ametropia and astigmatism. It is aimed to enroll (consent) approximately 110 subjects in approximately 8 sites in the United States, with a target of 15-22 treated subjects per site. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 3 weeks. Because a 10% screening failure rate is expected, approximately 110 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. Subject must be at least 18 years of age.
3. Willing and able to attend all scheduled study visits as required per protocol.
4. Successful wearer of toric soft contact lenses in both eyes for a minimum of 5 days per week and 10 hours per day during the past 3 months.

[redacted]

8.2 Exclusion Criteria

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

1. Current/previous PRECISION1 for Astigmatism and 1-Day Acuvue Moist for Astigmatism contact lens habitual wearers and any current spherical monovision and multifocal contact lens wearers.

[redacted]

[redacted]

11. 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.

[redacted]

Women of childbearing potential or women who are pregnant at the time of study entry are not excluded from participation. See Section 11.7 for further details regarding pregnancy in this study.

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 for Astigmatism contact lenses, Alcon

Control Product(s) (If applicable): 1-DAY ACUVUE MOIST for ASTIGMATISM, Johnson & Johnson

Table 9-1 Test Product

Test Product	PRECISION1 for Astigmatism contact lenses (P1fA) [redacted]
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 USA
Indication for use and intended purpose in the current study	**PRECISION1 for Astigmatism (verofilcon A)** toric soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with nondiseased eyes with 6.00 D or less of astigmatism. The lenses are lenses are intended to be worn once (daily disposable wear) and then discarded at the end of each wearing period. Within the current study the lenses will be used according to their approved intended purpose and indications for use.

Product description and parameters available for this study	• Material: verofilcon A
	• Water content: 51%
	• Power range:
	  ○ Sphere: -0.75 to -4.00 D in 0.25 D steps
	  ○ Cylinder: -0.75 D and -1.25 D
	  ○ Axis: 10º, 80º, 90º, 100º, 170º, and 180º
	• Base curve (mm): 8.5
	• Diameter (mm): 14.5
	• Other: N/A

Formulation	Refer to package insert

Usage	• Wear:
	  ○ Daily Disposable Wear
	  ○ Bilateral
	• Replacement period: Daily Disposable
	• Exposure: At least 10 hours per day, every day. [redacted]
	• Lens Care: N/A

Number/Amount of product to be provided to the subject	A sufficient amount of lenses will be dispensed at Visit 2 and Visit 3 to each subject to be replaced daily from the dispense visit until the scheduled follow-up visit.
Packaging description	Blister foil pack.

Labeling description	• Lens Foil label includes:
	  - material name and identifier
	  - base curve
	  - diameter
	  - packing solution
	  - power
	  - lot number
	  - expiration date
	  - content statement
	  - investigational device statement
	  - sponsor information
	• Provided in cartons of approximately 12 lenses per power per carton, identified with the following:
	  - a color coded label stating the protocol number
	  - material identifier
	  - power
	  - an investigational use only statement
	  - tracking number

Storage conditions	Stored at room temperature.

Supply	[redacted] • Based on the investigator's lens order form, the sponsor will send study lenses to the site for each subject. The site will provide the study lenses to the subject at Visit 2 and Visit 3. Refer to the MOP for a detailed description.

Table 9-2 Control Product

Control Product(s)	1-DAY ACUVUE MOIST for ASTIGMATISM, Johnson & Johnson [redacted]
Manufacturer	Johnson & Johnson Vision Care, Inc. 7500 Centurion Parkway Jacksonville, FL 32256 USA
Indication for Use	1-DAY ACUVUE MOIST for ASTIGMATISM contact lenses are indicated for daily disposable wear for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with nondiseased eyes who may have 0.50 to 3.00 D of astigmatism. The lenses contain a UV blocker to help protect against transmission of harmful UV radiation to the cornea and into the eye. When prescribed for daily disposable use, no cleaning or disinfection is required. Lenses should be discarded upon removal. Within the current study the lenses will be used according to their approved intended purpose and indications for use.

Product description and parameters available for this study	• Material: etafilcon A
	• Water content: 58%
	• Power range:
	  ○ Sphere: -0.75 to -4.00 D in 0.25 D steps
	  ○ Cylinder: -0.75 D and -1.25 D

	○ Axis: 10º, 80º, 90º, 100º, 170º, and 180º • Base curve (mm): 8.5 • Diameter (mm): 14.5 • Other: N/A
Formulation	Refer to package insert.
Usage	• Wear: ○ Daily Disposable Wear ○ Bilateral • Replacement period: Daily Disposable • Exposure: At least 10 hours per day, every day. [redacted] • Lens Care: N/A
Number/Amount of Product to be Provided to the subject	A sufficient amount of lenses will be dispensed at Visit 2 and Visit 3 to each subject to be replaced daily from the dispense visit until the scheduled follow-up visit.
Packaging description	Blister foil pack.
Labeling description	• Lens Foil label includes: - material name and identifier - base curve - diameter - packing solution - power - lot number - expiration date - content statement - investigational device statement - sponsor information • Provided in cartons of approximately 12 lenses per power per carton, identified with the following: - a color coded label stating the protocol number - material identifier

	- power - an investigational use only statement - tracking number
Storage conditions	Stored at room temperature.
Supply	[redacted] • Based on the investigator's lens order form, the sponsor will send study lenses to the site for each subject. The site will provide the study lenses to the subject at Visit 2 and Visit 3. Refer to the MOP for a detailed description.

More information on the test product can be found in the P1fA Package Insert; information on the control product can be found in the AMfA Package Insert.

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

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

9.3 Treatment Assignment / Randomization

Subjects will be randomized in a 1:1 ratio to receive treatment in crossover sequence as follows:

Sequence	EDC/randomization integration system	Lens Name
Sequence 1	[redacted]	P1fA/AMfA
Sequence 2	[redacted]	AMfA/P1fA

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 (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.

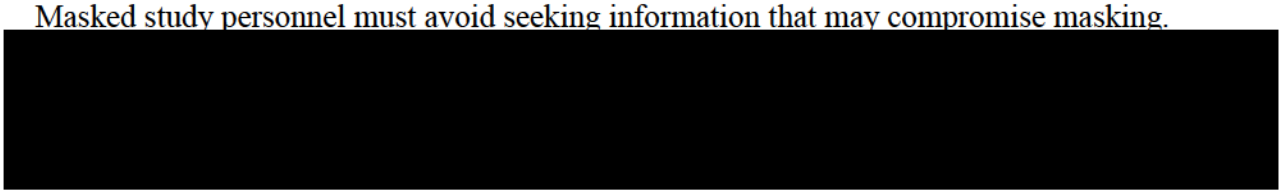
At Visit 1, all eligible subjects will be randomized via the EDC/randomization integration system to one of the treatment lens sequences. The investigator's delegate will access the respective system after confirming that the subject meets all the eligibility criteria. A randomization number will be automatically assigned to the subject according to the subject randomization list but will not be communicated to the site user. The EDC/randomization integration system will inform the site user of the treatment lens sequence assignment to be dispensed to the subject.

9.4 Treatment masking

This study is double-masked, with subjects randomized to use P1fA or AMfA in a crossover fashion for approximately 1 week each. [redacted]

This level of masking will be maintained throughout the conduct of the study. 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.



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. 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.

9.5 Accountability Procedures

Upon receipt of the IPs, the investigator's delegate must conduct an inventory. During the study, unmasked 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.

It is the investigator's responsibility to ensure that:

- All study products are accounted for and not used in any unauthorized manner
- All used foils and unused supplies are returned by each subject
- 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 source documents.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 Informed Consent and Screening

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

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

10.2 Description of Study Procedures and Assessments

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

10.2.1 Demographics

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

10.2.2 Medical History

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, including those associated with changes in concomitant medication dosing since the previous visit in the

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

10.2.5 Slit Lamp Biomicroscopy: Safety Assessment

Biomicroscopy examination of the cornea, conjunctiva, iris/anterior chamber, and lens must be performed in both eyes before instillation of any diagnostic eye drops (dye).

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 manufacturer's guidelines.

10.3 Unscheduled Visits

If a subject visit occurs between any regularly scheduled visits, this visit must be documented as an Unscheduled Visit. During all unscheduled visits, the investigator must conduct the following procedures:

- Collect Adverse Event information
- Record changes in medical condition or concomitant medication

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, as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

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

The investigator must document the reason for screen failure in the subject's 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 form.

Subject numbers of discontinued subjects must not be re-used.

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.

For subjects discontinuing from the study, the investigator must complete all Exit procedures according to Table 3-1, 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 source documents.

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

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

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

10.5 Clinical Study Termination

The study sponsor reserves the right to close the investigational site 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.

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

Comprehensive adverse event data will be collected in the subject source records. All AEs will be reported in the eCRF; however, adverse event details collected will be determined based on the type of AE (ocular or systemic), if serious criterion is met, relationship to the IP, or if a subject discontinues due to the AE. Further instructions for reporting are detailed in the MOP and the CRF completion guidelines.

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test product). Refer to the Glossary of Terms and figures below for categories of AEs and SAEs.

Figure 11-1 Categorization of All Adverse Events

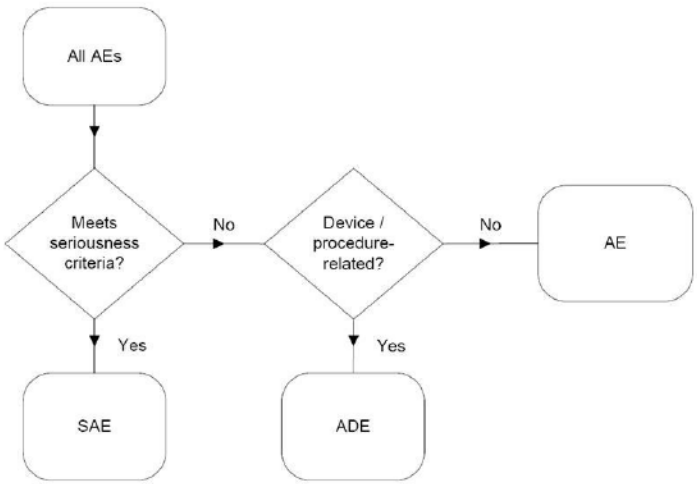
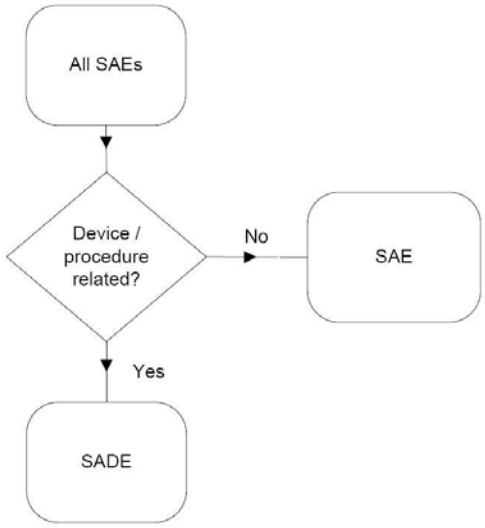


Figure 11-2 Categorization of All Serious Adverse Events



Device Deficiencies

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 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 cloudy
- Lens surface/edge defect
- Torn lens during handling/in pack
- Packaging deficit (e.g., mislabeled product)
- Suspect product contamination
- Lack of performance

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 since your last study visit?"

In addition, changes in *any protocol-specific parameters and/or questionnaires* evaluated during the study are to be reviewed by the investigator. Any untoward (unfavorable and unintended) change in *a protocol-specific parameter or questionnaire response* that is clinically relevant, in the opinion of the investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent Any 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 control 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 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 Adverse Device Effect (for related AEs) and *Serious Adverse Event* 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 [redacted] for US according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

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

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

Intensity and Causality Assessments

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

Intensity (Severity)

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

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

Causality

Related	An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.
Not Related	An AE classified as not related may either be definitely unrelated or simply unlikely to be related (i.e., there are other more likely causes for the AE).

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

11.4 Return Product Analysis

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

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 (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. If the treatment code needs to be broken in the interest of subject safety, the investigator is encouraged to contact an appropriate study sponsor representative prior to unmasking the information if there is sufficient time. Dependent upon the individual circumstances (i.e., medical emergency), the code may be broken prior to contact with the study sponsor. The study sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the study sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

11.6 Follow-Up of Subjects with Adverse Events

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

The investigator should provide the study sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ ongoing at time of 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).

All complaints received after this time period will be considered and processed as spontaneous (following the post market 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 (i.e., 1-DAY ACUVUE MOIST for ASTIGMATISM) directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

11.7 Pregnancy in the Clinical Study

Women of childbearing potential or women who are pregnant at the time of study entry are not excluded from participation. Pregnancy should be included in the Pregnancy eCRF 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 evaluated in this study.

[redacted]

12.3 Demographic and Baseline Characteristics

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

12.4 Effectiveness Analyses

This study defines 1 primary, [redacted] effectiveness endpoint. All effectiveness evaluations will use the FAS as the primary analysis set. Supportive analyses of the primary and key exploratory effectiveness endpoints will be conducted using the PP analysis set only if the number of subjects excluded from the PP analysis set exceeds 5% of the FAS.

The primary effectiveness endpoint of distance VA will be tested at one-sided $\alpha = 0.05$ for noninferiority [redacted]

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to demonstrate noninferiority in the VA at distance when wearing P1fA contact lenses compared to AMfA contact lenses. The primary endpoint is distance VA with study lenses, collected for each eye in logMAR.

12.4.1.1 Statistical Hypotheses

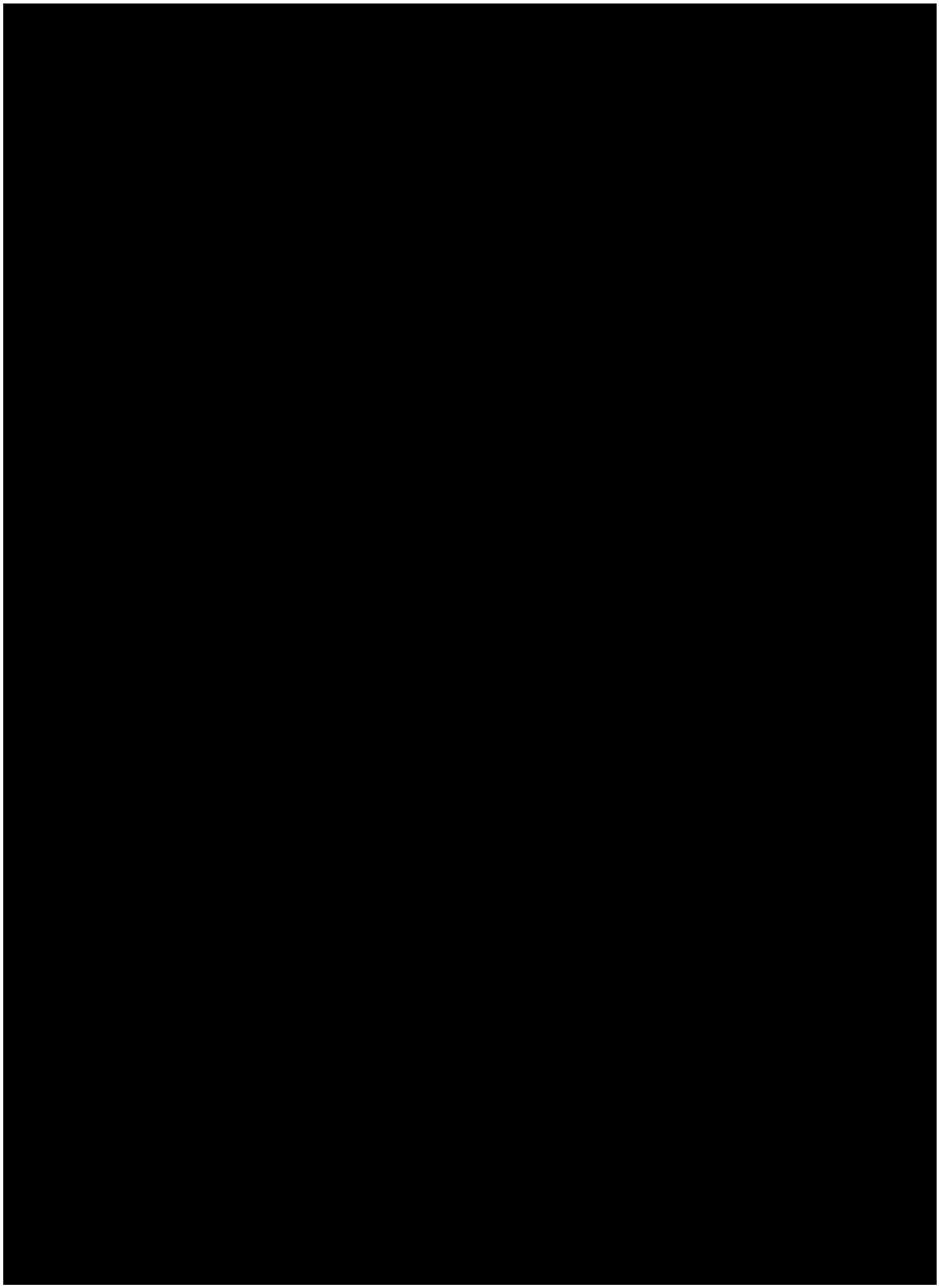
The null and alternative hypotheses are formulated in terms of the predefined margin of 0.05 for noninferiority:

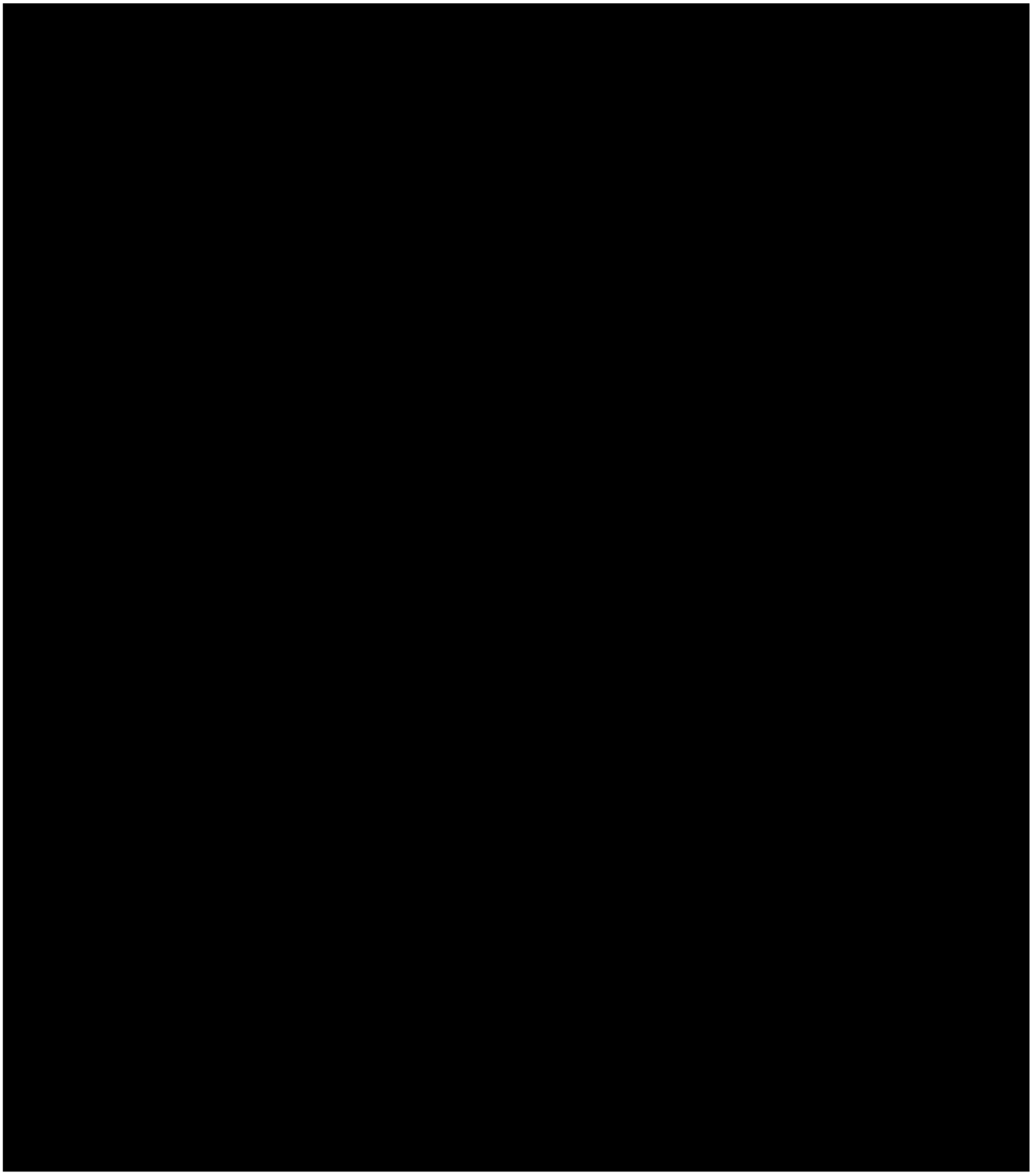
$$H_0: \mu_{(T)} - \mu_{(C)} \geq 0.05$$
$$H_a: \mu_{(T)} - \mu_{(C)} < 0.05$$

where $\mu_{(T)}$ and $\mu_{(C)}$ denote the mean distance VA for P1fA and AMfA, respectively, on the logMAR scale.

12.4.1.2 Analysis Methods

A mixed effect repeated measures model will be utilized to test these hypotheses. The model will include terms for lens, visit, lens by visit interaction, period, and sequence. Within-subject correlation due to eye and the crossover design will also be accounted for in the model. Lens difference (P1fA minus AMfA) 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.





12.5 Handling of Missing Data

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out for the primary and key exploratory 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 (MedDRA) Preferred Terms. AEs leading to study discontinuation, significant nonserious AEs, and SAEs will be identified. Individual subject listings will be provided, as necessary.

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

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

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

No inferential testing will be conducted for the safety analyses.

12.7 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.

12.8 Sample Size Justification

Sample size calculation is based on a prior clinical study [redacted] which evaluated performance of P1fA and AMfA.

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 0.0629 for paired differences, 80% power can be attained with a sample size of 12 (6 per sequence).

[redacted]

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The investigator must ensure that the subject's anonymity is maintained 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. At the end of the clinical study, the study sponsor will collect a copy of the enrollment log ***without any identifying subject information***. All documents submitted to the study sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information will be transmitted to the study sponsor.

The study sponsor may release anonymized study data to external researchers for purposes of future research directly related to the study objectives, or future research that is beyond the scope of the current study objectives. The Informed Consent Form explains this to study subjects. Anonymization means that all identifiable information will be removed from the dataset and all links to the subjects in the study will be removed. Anonymization of the data will maintain confidentiality of the subjects who participate in the study so that they cannot be identified by external researchers. The anonymized data set will contain records from all of the subjects in the current study, but the anonymization process might change the data set in some ways, so external researchers will be informed that they might not be able to duplicate some of the results from this study.

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 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, fax, and electronic correspondence. Close-out visits will take place after the last visit of the last subject at the site.

A CI 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

This clinical study must be conducted in accordance with the ethical principles contained within:

- The Declaration of Helsinki, and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155:2011, and the applicable US FDA 21 CFR Regulations.
- SOPs of the study sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations.
- 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 and the process 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 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 as 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 as required by current regulations and, if applicable, in other public databases as required by local country regulations.

15 REFERENCES

- 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