A Single-Arm Study to Evaluate and Demonstrate Safety and Performance of a Novel Ocular Lubricant in Adult Subjects with Dry Eye Disease

STUDY ID

DEP918-C001

PROTOCOL v.3

27 August 2024

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Alcon

Clinical Study Protocol

Study Title:	A Single-Arm Study to Evaluate and Demonstrate Safety and Performance of a Novel Ocular Lubricant in Adult Subjects with Dry Eye Disease
Study Short Name:	Study of Safety and Performance of a Novel Ocular Lubricant in Subjects with Dry Eye Disease
Study Number:	DEP918-C001
Study Phase:	3
Product Name:	FID123300
Indication:	For the temporary relief of burning and irritation in persons experiencing dry eye symptoms.
Investigators:	Multicenter, located in the United States
Sponsor:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099, US

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described study in compliance with Good Clinical Practice (GCP), the ethical medical research principles contained within the Declaration of Helsinki, this protocol, all applicable laws, regulatory authority regulations, and conditions of approval imposed by the reviewing IRB/IEC or regulatory or governmental authority.
- I will supervise all testing of the Investigational Product(s) involving human research subjects and ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met in accordance with applicable local and governmental laws and regulations.
- I have read and understand the appropriate use of the Investigational Product(s) as described in the protocol, current IB, 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 applicable government laws and 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:

AMENDMENT DETAILS

History of Amendments

This is the third version of the protocol. Amendment 2.

Document	Sponsor Approval Date (DD/Mmm/YYYY)
Amendment 1	13/Aug/2024
Original protocol	10/May/2024

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1 GLOSSARY OF TERMS

Table 1-1 List of Terms

Term	Definition
Adverse Drug Reaction (ADR)	All noxious and unintended responses to an investigational product related to any dose should be considered adverse drug reactions. Responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
Adverse Event (AE)	Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
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.*
Enrollment	A human subject's, or their legally authorized representative's, agreement to participate in a clinical trial following completion of the informed consent process, as required in 21 CFR part 50 and/or 45 CFR part 46, as applicable. For the purposes of this part, potential subjects who are screened for the purpose of determining eligibility for a trial, but do not participate in the trial, are not considered enrolled, unless otherwise specified by the protocol. A subject is enrolled at the time point they begin receiving the study investigational product.
Interventional Clinical Trial	Clinical trial in which subjects are assigned to groups that receive one or more intervention/treatment (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study's protocol. Subjects may receive diagnostic, therapeutic, or other types of interventions.
Investigational Product	A preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or comparator product in a clinical study, 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

Term	Definition
	unauthorized indication, or when used to gain further information about the authorized form.
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Point of Enrollment	The time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject sign and dates the informed consent form.
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study.
Screening	A process of active evaluation of potential subjects for enrollment in a study. After a patient is recruited, screening occurs during the enrollment period, after informed consent has been obtained, to see if they meet the inclusion and exclusion criteria. If they meet the criteria, the subject is eligible to enroll in the study.
Serious Adverse Event (SAE)	Any untoward medical occurrence that at any dose: results in death, is life-threatening, *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.* requires inpatient hospitalization or prolongation of existing hospitalization, *Note: Planned hospitalization for a preexisting condition, without serious deterioration in health, is not considered a serious adverse event.* results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event or reaction. *Note: Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.*

Term	Definition
	Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
Serious Adverse Reaction (SAR)	Adverse drug reaction that has resulted in any of the consequences characteristic of a serious adverse event.
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 study, whichever is later.
Study Start	The start of the study is considered to coincide with the enrollment of the first patient.
Subject	A study participant
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Adverse drug reaction that is both unexpected and meets the definition of a serious adverse event.
Unexpected Adverse Drug Reaction (Unexpected ADR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved investigational product or Company Core Data Sheet and/or package insert/summary of product characteristics for an approved product).

Table 1-2 List of Acronyms and Abbreviations

Abbreviation	Definition
ADDE	Aqueous deficient dry eye
ADR	Adverse drug reaction
AE	Adverse event
AR	Adverse reaction
BCVA	Best corrected visual acuity
°C	Degrees Celsius
CI	Confidence intervals
CL	Confidence limits
CONSORT	Consolidated standards of reporting trials
CRF	Case Report Form
CRO	Contract Research Organization
DED	Dry eye disease

Abbreviation	Definition
DEP	Data evaluability plan
DES	Dry eye symptom
[redacted]	[redacted]
EC	Ethics Committee
eCRF	Electronic case report form
ePRO	Electronic patient reported outcomes
EDC	Electronic data capture
EDE	Evaporative dry eye
EN	European Standard
EU	European Union
ETDRS	Early Treatment Diabetic Retinopathy Study
FID	Formulation identification
GCP	Good Clinical Practice
Hr	Hour(s)
ICE	Intercurrent event
ICF	Informed consent form
IB	Investigator's brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDEEL-SB	Impact of Dry Eye on Everyday Life- Symptom Bother
IEC	Independent Ethics Committee
IFU	Instructions for use
IP	Investigational product
IRB	Institutional Review Board
LogMAR	Log of the minimum angle of resolution
MDE	Mixed dry eye
mL	milliliter
[redacted]	[redacted]
MOP	Manual of procedures
N/A	Not applicable
[redacted]	[redacted]
OD	Right eye
OS	Left eye
OTC	Over the counter

Abbreviation	Definition
PP	Per Protocol
SAE	Serious adverse events
SAR	Serious adverse reaction
SD	Standard deviation
SLE	Slit lamp examination
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
US	United States

2 PROTOCOL SUMMARY

2.1 Protocol Synopsis

Compound Number(s):	FID123300
Study Phase:	Phase 3
Brief Summary of Protocol:	A 30-day prospective, single-arm, multicenter, open label study to demonstrate efficacy and safety of a novel lubricant eye drop in adult patients with mild to moderate dry eye disease (DED).

2.1.1 Primary and Safety Objectives and Endpoints

Table 2-1 lists the objectives and endpoints. For more information, see Section 4.

Table 2-1 Primary and Safety Objectives and Endpoints

Primary Objective To demonstrate efficacy of a novel lubricant eye drop	Primary Endpoint Change from baseline in Impact of Dry Eye on Everyday Life - Symptom Bother (IDEEL-SB) questionnaire score at Day 30
Safety Objective To evaluate safety of a novel lubricant eye drop	• Adverse events • BCVA • Biomicroscopy findings • Device deficiencies

2.1.2 Overall Design

Several key aspects of the study design are summarized below.

Intervention Model:	Single group
Control:	None/uncontrolled
Active Comparator:	N/A
Interventional Product Assignment Method:	All subjects will receive the same investigational product (IP)
Population Type:	Adult subjects
[redacted]	
Population Age:	Minimum: 18 – Maximum: N/A
Number of Subjects:	~185 enrolled
Number of Arms:	1
Site Distribution:	Planned number of clinical sites: ~ 20 Planned locations: United States

2.1.3 Arms and Duration

Total duration of study participation for each subject: approximately 37 days.

2.1.4 Masking

The following roles indicated below will not be made aware of the intervention assignment during the study:

- N/A (no masking)

For more information on masking, see Section 7.6.

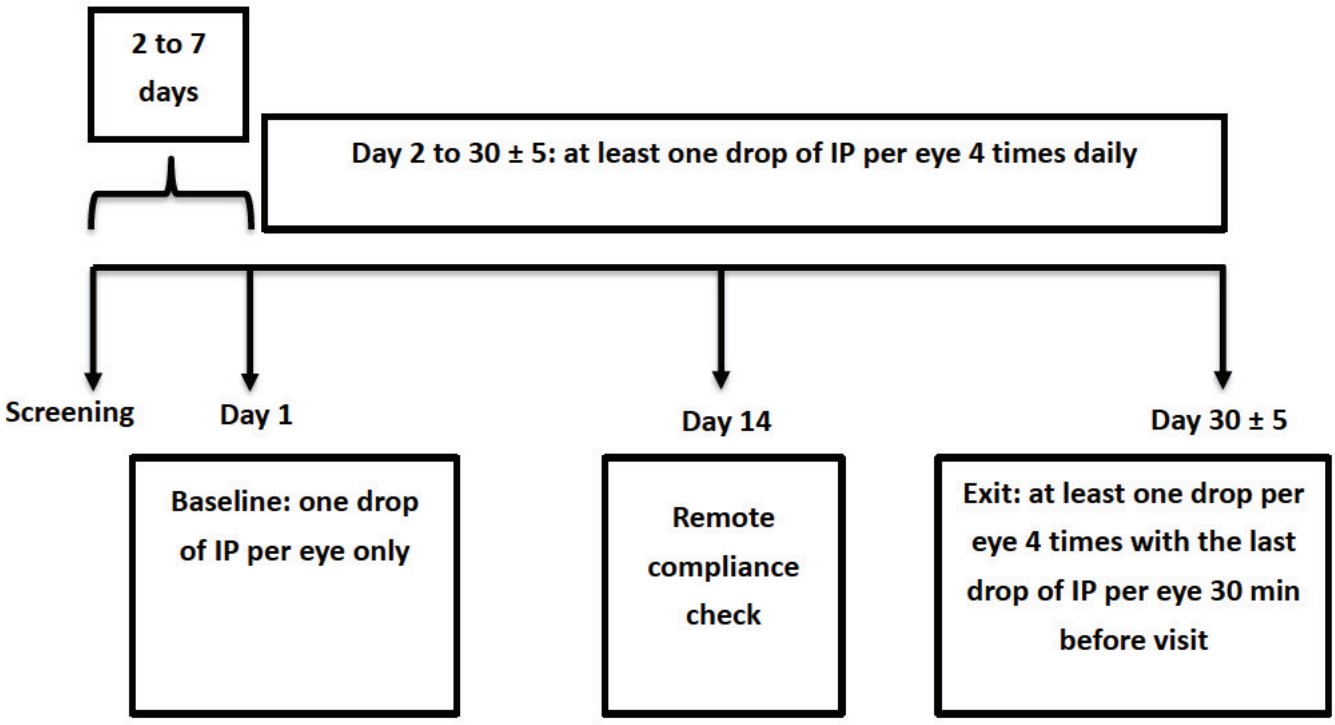
2.1.5 Committees

N/A

2.2 Study Schema

Figure 2-1 illustrates the study design.

Figure 2-1 Study Design



2.3 Schedule of Study Procedures and Assessments

Table 2-2 provides a summary of the schedule of study procedures and assessments.

Table 2-2 Schedule of Study Procedures and Assessments

Visit	Visit 1 Screening	Visit 2 Baseline	Visit 3 Remote Compliance Check	Visit 4 Exit	Unscheduled Visit	Early Exit
Study Day and Visit Window	**2 to 7 days prior to Visit 2**	**Day 1**	**Day 14 ± 3 days**	**Day 30 ± 5 days**		
Informed consent	X					
Connect to electronic patient reported outcomes	X[9]	X		X	(X)	X
Demographics	X					
Medical history	X					
Concomitant medications	X					
Changes to concomitant medications or medical history		X	X	X	X	X
Urine pregnancy test[1]	X			X	(X)	X
Inclusion/exclusion	X					
Meibomian gland functionality test[1]	X					
BCVA (OD, OS; logMAR; distance)	X	X		X	(X)	X
IDEEL-SB Questionnaire[8]	X			X		X
[redacted]						

Visit	Visit 1 Screening	Visit 2 Baseline	Visit 3 Remote Compliance Check	Visit 4 Exit	Unscheduled Visit	Early Exit
Study Day and Visit Window	**2 to 7 days prior to Visit 2**	**Day 1**	**Day 14 ± 3 days**	**Day 30 ± 5 days**		
[redacted]						
Slit lamp biomicroscopy examination (with corneal staining)	X	X		X	X[7]	X
Administer IP (IP instillation on site)		X				
[redacted]						
Adverse events	X	X	X	X	X	X
Device deficiencies	X	X	X	X	X	X
[redacted]						
Distribute subject instructions		X			(X)	
Dispense IP		X			(X)	
Collect used and unused IP				X	(X)	X
Remote compliance check			X			

(X) Assessments performed as necessary

[1] Source Only

[redacted]

[redacted]

[7] Assessment performed as necessary for unplanned dispense visit

[8] Electronic patient reported outcomes unless otherwise specified by sponsor

[9] Screening may be rescheduled within 7 days/1 week if connection cannot be established. All remaining criteria will be verified after completing connection.

3 INTRODUCTION

3.1 Purpose of Study

The novel formulation (FID123300) is aimed at providing long-lasting comfort to patients with dry eyes. The study is designed to evaluate and demonstrate the efficacy and safety of this investigational ocular lubricant formulation in patients with mild to moderate DED.

Endpoints include safety assessments (AEs, BCVA, slit lamp biomicroscopy, and device deficiencies), subjective assessment of symptoms of dry eye (IDEEL-SB [redacted].

Refer to Sections 2.2 and 2.3 for more information.

3.2 Summary of Benefits and Risks

3.2.1 Benefit Summary

The key benefit expected from the novel ophthalmic lubricant is the temporary relief of dry eye symptoms in patients with dry eye similar to other currently marketed dry eye drops such as SYSTANE COMPLETE Lubricant Eye Drops [redacted] and SYSTANE HYDRATION Lubricant Eye Drops [redacted]

SYSTANE COMPLETE Lubricant Eye Drops [redacted]) and SYSTANE HYDRATION Lubricant Eye Drops [redacted] are indicated for the temporary relief of burning and irritation due to dryness of the eye. SYSTANE HYDRATION Lubricant Eye Drops may be used to lubricate and rewet daily, extended wear and disposable silicone hydrogel and soft (hydrophilic) contact lenses.

Benefits of a lubricant eye drop include ocular surface protection, dry eye relief, improved visual performance, increased ocular surface retention and lubrication. It also allows re-epithelialization of cells in the ocular surface.

3.2.2 Risk Summary and Mitigation Strategy

Risk management principles have been applied to both the planning and the intended conduct of the clinical investigation, in order to ensure the reliability of the clinical data generated and the safety of the subjects. The clinical investigation process risks are managed through appropriate training and monitoring according to the protocol-specific monitoring plan. IP

risks, including risks associated with use of IP and methods and procedures for application of the IP, are defined in the IB and/or product labeling and are managed through review of safety assessments outlined in this protocol.

The ingredients in the test formulation are biologically inert (i.e., they have no known on-target or off-target biological mechanisms of action). Therefore, no dose-dependent side effects are anticipated. The risks of administering a viscous topical ocular drop include mild transient blurred vision and ocular discomfort. Due to subject variability, there is a risk of allergic reaction to one or more of the components of the test formulation. Patients with any known allergies to any of the components of the formulation are excluded from participation in clinical studies. These anticipated risks are similar to other currently available dry eye drops such as SYSTANE COMPLETE Lubricant Eye Drops [redacted] and SYSTANE HYDRATION Lubricant Eye Drops [redacted].

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

3.2.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk for subjects involved in this study, the potential risks identified in association with FID123300 are justified by the anticipated benefits that may be afforded to subjects for the temporary relief of burning and irritation in persons experiencing dry eye symptoms.

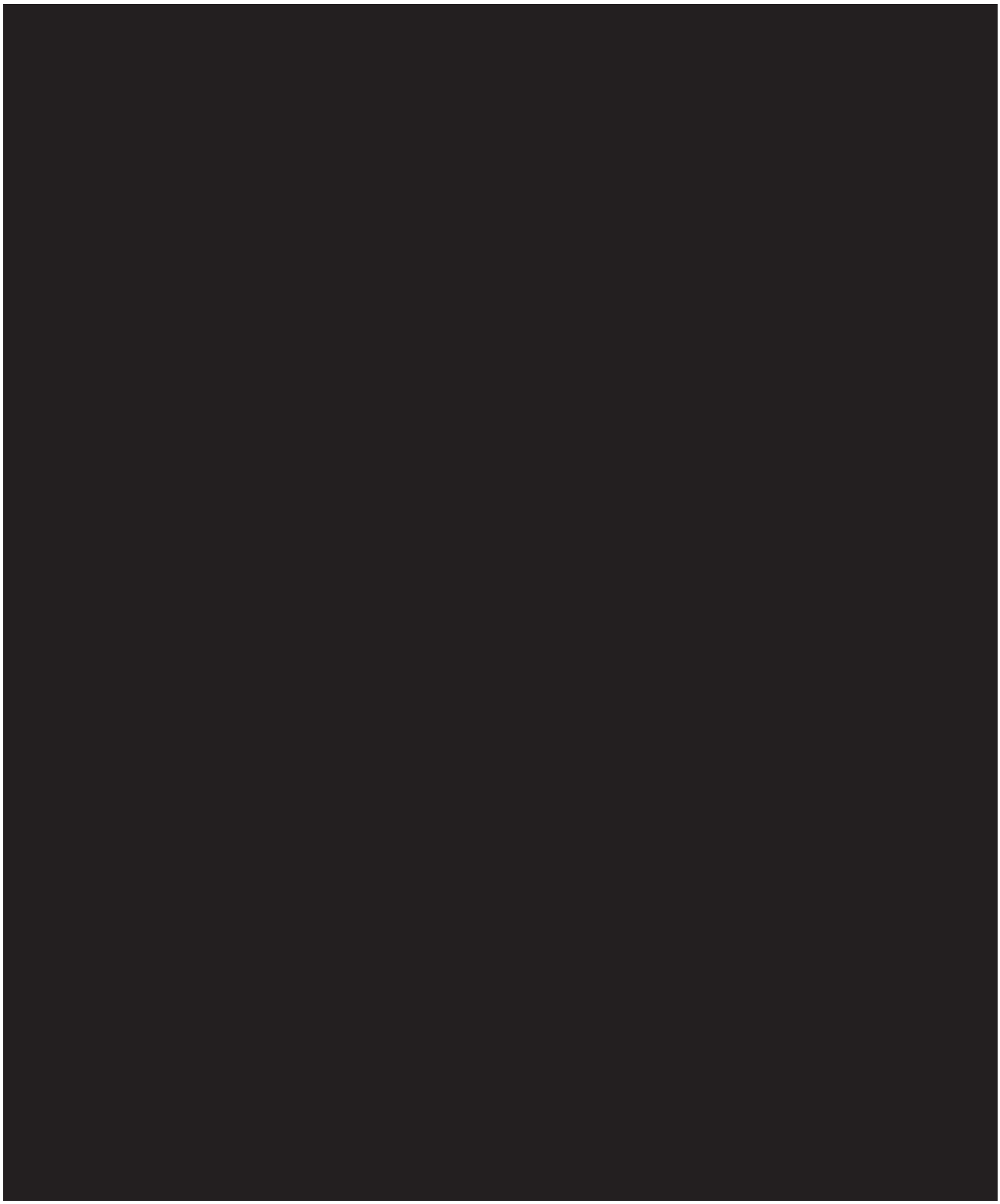
More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) and device deficiencies of FID123300 may be found in the IB.

4 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMANDS

4.1 Primary Objective(s)

Table 4-1 Primary Objectives and Endpoints

Objective(s)	Endpoint(s)
To demonstrate efficacy of a novel lubricant eye drop	Primary • Change from baseline in Impact of Dry Eye on Everyday Life – Symptom Bother (IDEEL-SB) questionnaire score at Day 30



4.2 Primary Estimand

The treatment effect is to be estimated for the population of adult patients with mild to moderate DED as defined by the protocol inclusion/exclusion criteria. The efficacy is to be

measured using the primary endpoint of the change from baseline in IDEEL-SB questionnaire score at Day 30.

In this single-arm study, an intercurrent event (ICE) may occur with subjects exposing to a concomitant medication or discontinuation of IP (permanent or temporary; due to an AE, device deficiency, and/or noncompliance).

The population-level summary is the mean change from baseline in IDEEL-SB questionnaire score at Day 30, where baseline is defined as the data collected at Visit 1 prior to IP exposure. Change from baseline will be calculated as Day 30 minus baseline.

4.3 Secondary Objective(s)

N/A

4.4 Secondary Estimand

N/A

5 STUDY DESIGN

5.1 Description of Study Design

This is a phase 3, multicenter, uncontrolled, open label, nonrandomized study conducted at approximately 20 sites in the US. Approximately 185 subjects will be enrolled. All eligible subjects will have mild to moderate DED (inclusion criteria number 4).

5.1.1 Description of Study Duration

The study is expected to be completed in approximately 7 months. The expected study duration for each subject is 37 days with 30 ± 5 days of IP exposure.

The study will consist of a Screening visit, Baseline visit on Day 1, Remote Compliance Check on Day 14, and an Exit visit on Day 30.

Refer to Section 2.2 for more information and Figure 2-1 for an outline of the study.

[redacted]

5.2 Rationale for Study Design

This study is designed to evaluate the efficacy and safety of FID123300 in adult patients with mild to moderate DED. The primary endpoint of change in IDEEL-SB score was selected to fulfill the primary objective of the study. Procedures for measurement of these endpoints were selected based on dry eye clinical assessments and tests conducted in clinical practice and dry eye research studies. The design of this study is justified based upon preclinical and clinical testing, as described within the IB.

The registration of the IP in the US as an over the counter (OTC) product monograph does not require the conduct of a clinical study to be performed prior to the product being marketed. However, at the time of the first launch of this product, there will be preclinical data and data from similar OTC products to understand how patients respond to the new formulation. [redacted]

6 STUDY POPULATION

6.1 Selection of Study Population

The study population consists of male and female subjects (age ≥ 18) at the time of informed consent. Subjects must have a clinical diagnosis of mild to moderate DED. The study is aimed to enroll approximately 185 subjects in approximately 20 sites in the US, with a target of 143 completed subjects. Estimated time needed to recruit subjects for the study is approximately 20 weeks; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol. Because a 20-30% screening failure rate is expected, approximately 185 subjects are expected to be enrolled.

Subjects will be recruited by clinical sites that have DED patients. Additional recruitment methods may be employed as needed as determined/provided/approved by sponsor or at each site's discretion.

Selected population according to the inclusion/exclusion criteria is representative of the target population for the product.

6.2 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing the 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 at least 18 years of age at the time of informed consent.
2. Subject must be willing and able to understand and sign an IRB/IEC approved informed consent form.
3. Subject must be willing and able to attend all required study visits and complete subjective questionnaires.
4. Subject must exhibit symptoms of dry eye at the Screening visit (IDEEL- SB ≥ 16 and ≤ 65).
5. Subject must have BCVA equal to or better than 20/80 (or ≥ 55 letters score or ≥ 0.6 ETDRS logMAR) in each eye at the Screening visit.
6. Subject must have NITBUT of > 5 and < 10 seconds in each eye at the Screening visit.
7. Subject must meet at least one of the 3 conditions below at the Screening visit (based on the criteria below):
    a. ADDE as indicated by a TMH of < 0.2 mm
    b. EDE as indicated by a meibum quality score of ≥ 1 (on a 0 to 3 scale) or meibum expressibility score of > 1 (on a 0 to 3 scale) in either eye lid (lipid deficient (or evaporative) dry eye subgroup) measured by the Meibomian Gland Functionality Test.
    c. MDE as indicated by meeting both entry criteria (a) and (b) above (mixed dry eye subgroup).
8. Subject must be willing to discontinue use of all artificial tear supplements and use only the study product as directed starting at Visit 2/Day 1.
9. Subject must be willing and able to connect to and use electronic patient reported outcomes with their mobile device to [redacted] record daily IP usage information.

[redacted]

6.3 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded and may not participate in this study. Criteria are assessed at Screening/Visit 1.

1. History of hypersensitivity to the study drug or any of its excipients or to drugs of similar chemical classes.
2. Women who are pregnant or breastfeeding at the time of study entry or who plan to become pregnant during the study.
3. Ocular abnormalities that could adversely affect the safety or efficacy outcome such as:
    a. Eyelid anomalies that affect proper lid closure or proper blink function (e.g., ectropion or entropion).
    b. Corneal disorders or abnormality such as active corneal ulcer, current corneal abrasion, keratoconus, or corneal dystrophies which are actively changing or affect vision.
    c. Metaplasia of the ocular surface.
    d. History of corneal erosion syndrome or recurrent corneal erosion syndrome.
    e. Clinically significant corneal epithelial anterior membrane dystrophy (patients with minor/insignificant primary peripheral corneal epithelial dystrophy (not central dystrophy) without a history of corneal erosion syndrome can be included).
    f. Current filamentous keratitis.
    g. Evidence of corneal neovascularization.
    h. Any history of herpes simplex or herpes zoster keratitis.
4. Uncontrolled active systemic diseases. These conditions may include but are not limited to conditions that in the opinion of the investigator would preclude study participation, including unstable diabetes, thyroid diseases, autoimmune diseases, and/or poorly controlled hypertension.

5. Active ocular infection (bacterial, viral, or fungal) or active inflammation not associated with dry eye such as uveitis, iritis, active blepharitis, active ocular allergies or active allergic conjunctivitis, etc.
6. Current or past participation in any clinical study within 30 days prior to the Screening visit.
7. Punctal plug insertion or diathermy procedure initiated within 30 days prior to the Screening visit.
8. Lid hygiene therapy initiated ≤ 4 weeks prior to the Screening visit. Note: Patients who have been on a consistent lid hygiene therapy (i.e., no change to the type of lid hygiene therapy being used or to the frequency of use) for more than 4 weeks prior to the Screening visit are not excluded. However, they cannot stop or change this regimen for the duration of the study. In addition, patients who do not currently use lid hygiene therapy cannot start the regimen while participating in the study.
9. Individuals who were treated with thermal pulsation treatments or other lid treatments in either eye in the last 12 months. Patients cannot be treated with thermal pulsation treatments or other lid treatments while participating in the study.
10. Any significant illnesses that could, in the opinion of the investigator, interfere with the study parameters.
11. Use of any systemic medication known to cause dry eye (e.g., antihistamines, antidepressants, antipsychotics, benzodiazepines, etc.) for less than 1 month before the Screening visit. If patient is on a stable regimen for at least a month prior to the Screening visit, the dosing regimen must not change for the duration of their participation in this study. In addition, patients who do not currently use any of these medications cannot start a regimen while participating in the study.
12. Contact lens use within one month prior to Screening visit and unwilling to avoid contact lens use during the course of the study.
13. History of ocular or intraocular surgery, eyelid surgery, keratorefractive procedure, corneal transplant, or serious ocular trauma, within 6 months prior to the Screening visit.
14. Initiation of any new topical ocular medication (over the counter or prescribed) ≤ 60 days prior to the Screening visit. Note: Patients on Restasis®, Cequa® (cyclosporine ophthalmic emulsion), or lifitegrast ophthalmic solution 5% (Xiidra®), must be on therapy for at least 6 months prior to the Screening visit.

6.4 Lifestyle Considerations

6.4.1 Other Activity

Subjects will be advised to maintain and be in a consistent environment and refrain from swimming on Day 1.

6.5 Screen Failures and Rescreening of Subjects

A screen failure occurs when a subject who consents to participate in the clinical study does not meet inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

Subjects will not be replaced.

After signing the informed consent form (ICF), subjects will be asked to establish a connection to the electronic patient reported outcomes (ePRO) (inclusion criteria number 9) prior to any other assessments. In the event this connection cannot be established, subjects will be allowed to reschedule the Screening visit within 7 days/1 week. All remaining criteria will be verified after completing inclusion criteria number 9. In case the subject is not willing to reschedule or the Screening visit can’t be rescheduled within the specified window, the subject will be considered a screen failure.

Enrollment number may be increased based on the tracking of number of completers.

6.6 Study Eye Selection Criteria

Study subjects will be dosed in both eyes.

7 INVESTIGATIONAL PRODUCT AND CONCOMITANT THERAPY

7.1 Description of Investigational Product

This study will investigate the IP in a single period. The expected duration of subject participation is approximately 37 days; IP exposure is approximately 30 ± 5 days. Visit 1/Screening will occur 2 to 7 days prior to Visit 2/Day 1 Baseline. At Visit 2/Day 1 Baseline,

subjects will administer one drop of IP per eye. [redacted] Starting on Day 2, subjects will administer at least one drop of IP per eye 4 times daily through to Visit 4/Exit. The Visit 3/Remote Compliance Check will occur on Day 14 ± 3 days [redacted] Visit 4/Exit will occur on Day 30 ± 5 days. On Visit 4/Exit, subjects will administer at least one drop of IP per eye 4 times with their last drop 30 minutes prior to the visit.

More information on the IP can be found in the IB.

7.2 Rationale for Investigational Product

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

7.3 Dosing and Administration

This study is evaluating the effect of 1) one ophthalmic drop of IP in each eye on Day 1 and 2) at least one ophthalmic drop of IP in each eye 4 times daily (additional usage as needed) after 30 ± 5 days on subjects with DED.

There are no time requirements within each day (e.g., morning, afternoon, night) for daily dosing from Day 2 to Day 30 ± 5. On Visit 4/Exit, subjects should administer one drop of IP in each eye 4 times with the last ophthalmic drop administered approximately 30 minutes prior the visit. Subjects should follow drop administration requirements. Instructions for delayed or missed drop administration will be outlined within the MOP/instructions.

Table 7-1 Dosing Regimen

Intervention:	FID123300
Dosing Regimen:	At Visit 2/Day 1, subjects will receive one drop of IP per eye in the morning. [redacted] On Days 2 to 30 ± 5 (including day of) subjects will self-administer at least

	one drop per eye 4 times daily. On Visit 4/Day 30 ± 5, subjects will self-administer at least one drop per eye 4 times with the last drop per eye approximately 30 minutes prior to Visit 4.

7.4 Treatment of Overdose

The components of this product are considered pharmacologically inert, non-toxic, and nonirritating. Therefore, no toxic effects are to be expected. For more information refer to IB.

7.5 Preparation, Handling, Storage, and Accountability

7.5.1 Preparation of Investigational Product

No special preparation is needed. Subjects will be dispensed two bottles at Day 1. If subjects require resupply, subjects should contact the site.

For more information refer to the IFU.

7.5.2 Handling and Storage of Investigational Product

Compound Number:	FID123300
Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, Texas 76134-2099 US
Indication for use and intended purpose in the current study	For the temporary relief of burning and irritation due to dryness of the eye
Product description and parameters available for this study	Propylene Glycol 0.6% Lubricant Eye Drops

Formulation	Refer to IB for details.
Number/Amount of product to be provided to the subject	Subject will receive two 11 mL bottles of IP with a 10 mL fill. Subjects will return to office for spare IP.
[redacted]	
Labeling description	Label shall include the information below, at minimum: • FID number • Lot number/batch number • Expiration date • Content statement • Investigational statement • Sponsor information • Temperature/storage conditions
Training and/or experience requirements for device	No additional training or experience is required to administer the IP.
Storage conditions	15 – 25°C (59 – 77°F) Refer to MOP for details regarding temperature monitoring.
Additional information	N/A
Supply	The IP will be provided by the study sponsor prior to the start of the study. Refer to the MOP for a detailed description.

7.5.3 Accountability of Investigational Product

The investigator must keep an accurate accounting of the number of IP units delivered to the site, dispensed to subjects, returned to the investigator by the subject, and returned to the sponsor or other disposition during and at the completion of the study.

7.5.3.1 Receipt of Investigational Product

Upon receipt of the IP, the investigator or delegate must conduct an inventory. During the study, the investigator or designated study staff must provide the IP to the subjects. 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 IP sent to the investigator must be accounted for by study sponsor personnel, and in no case be used in an unauthorized situation.

7.5.3.2 Return of Investigational Product

When the site is closed, the study is completed or is terminated by the sponsor, all unused IP will be returned to the sponsor (or the sponsor's designee). The investigator is responsible for proper disposition of all used IP at the conclusion of the study after IP reconciliation, according to the instructions provided in the MOP. All IP reconciliation procedures must be completed before the study is concluded. The responsible person at the investigator's institution must account for all used and unused IP. The IP storage manager or designee will complete a study drug returns form or equivalent that will be signed by the investigator or designee prior to returning the unused IP to the sponsor's designee.

7.6 Subject Assignment, Randomization, and Masking

7.6.1 Subject Assignment

Subject assignment is not applicable in this single-arm design, with one IP, as all subjects who meet the inclusion/exclusion criteria will receive the same IP.

7.6.2 Masking and Unmasking

All members associated with the study (at the site and the study sponsor) are unmasked to the assigned IP.

7.7 Investigational Product Compliance

Compliance with IP usage will be assessed at Visit 3/Remote Compliance Check and Visit 4/Exit. [redacted]

[redacted]

7.8 Concomitant Therapy

Pharmacologic and nonpharmacologic therapies and surgeries/procedures will be queried during Visit 1/Screening.

7.8.1 Prohibited Concomitant Therapy

The table below outlines all prohibited prior and concomitant therapies. Subjects must discontinue the use of any of the therapies or interventions listed in Table 7-2 for the specified period prior to the specified visit and these therapies or interventions must not be used during the course of the study. Use of any of these therapies or interventions during the course of the study must be documented as a protocol deviation.

Table 7-2 Prohibited Concomitant Therapies

Intervention/Therapy	Washout Required	Precaution(s) and Action(s) to be Taken	Rationale
Topical ocular medications preserved with benzalkonium chloride. Examples include: Travatan, Xalatan, Lumigan, etc.	A month before the Screening visit until subject is exited from the study.	Discontinue subject from study if taken concomitantly during IP administration.	May confound primary efficacy variable.
Any artificial tear products. Examples of prohibited ocular lubricants include: Blink, Refresh, Biotrue, other Systane products, iVizia, Visine, Soothe, etc. See exclusion criteria number 14 (Section 6.3)	From the beginning of the Baseline visit until subject is exited from the study.	Discontinue patient from study if any ocular lubricant is taken concomitantly with IP for more than 2 consecutive days.	May confound primary efficacy variable.

8 DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT WITHDRAWAL FROM STUDY

8.1 Discontinuation of Investigational Product

Discontinuation of IP for a Subject occurs when IP is stopped earlier than the protocol planned duration.

8.1.1 Criteria for Permanent Discontinuation of Investigational Product

A subject may be discontinued from IP at the discretion of the investigator or the medical monitor. Other reasons that a subject may be discontinued from IP may include, but are not limited to:

- *Adverse event(s) (AEs including, in the opinion of the investigator, clinically relevant laboratory abnormalities, and intercurrent diseases reported by the subject or observed by the investigator)
- ^Pregnancy

*AE may result in discontinuation of IP; however, it is up to discretion of the investigator if subject should continue safety assessments in the study.

^Pregnancies occurring in subjects enrolled in the study must be reported and followed to outcome. No further study treatments will be administered to pregnant subjects; however, the subject will be encouraged to complete all safety assessments in the study.

Subjects that discontinue IP and continue in the study should continue safety assessments.

8.1.2 Temporary Discontinuation or Interruption of Investigational Product

Subjects who have to interrupt treatment for any reason should be discontinued from participation in the study at the investigator's discretion. Subjects who miss a dose(s) of IP should resume administration at their earliest convenience [redacted] Subjects should aim to use the minimum required dosage.

Every effort must be made to keep the subject in the study and to continue with the study assessments as specified in to Table 2-2 and Section 2.3 until the final visit.

8.1.3 Rechallenge

Subjects that experience an AE and have discontinued IP will not be rechallenged. However, this does not apply to suspected or expected AEs (e.g., eye redness, ocular discomfort, or temporary blurring of vision) that are reported without subject discontinuation/will not be considered rechallenged.

8.2 Subject Withdrawal from the Study

A subject may exit the study by their own volition. Any subject may decide to voluntarily withdraw from the study at any time without prejudice. The sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If possible, an early exit visit should be conducted, in accordance with to Table 2-2 and Section 2.3. IP will be discontinued upon subject exit.

The investigator must document the reason for study or IP 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.

A subject may be withdrawn from the study at the discretion of the investigator or the medical monitor. Other reasons that a subject may be withdrawn from the study may include, but are not limited to:

- Adverse event(s) (AEs including, in the opinion of the investigator, clinically relevant laboratory abnormalities, and intercurrent diseases reported by the subject or observed by the investigator)
- Death
- Lack of efficacy
- Lost to follow-up
- Pregnancy
- Protocol violation (specify)
- Study terminated by sponsor
- Technical problems
- Withdrawal by subject (specify)
- Other (specify)

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.4 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.

8.5 Study Stopping Rules

N/A

9 STUDY ASSESSMENTS AND PROCEDURES

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

9.1 Screening/Baseline Assessments and Procedures

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 ICF. 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 ICF.

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.

9.1.1 Connect to Electronic Patient Reported Outcomes

At Screening, subjects must connect to ePRO with their mobile device after signing the ICF and prior performing any other assessments. If subject is unable to connect, the Screening visit can be rescheduled within a maximum of 7 days/1week to allow the subject to meet inclusion criteria number 9. All remaining eligibility criteria will be verified after completing inclusion criteria number 9.

9.1.2 Demographics

Obtain relevant demographic information including age, race, ethnicity, sex, etc.

9.1.3 Medical/Ophthalmic History

Significant medical and ophthalmic history will be collected at Screening, including:

- Current medical/ophthalmic conditions
- Medical/ophthalmic conditions that began within the last 12 months and which may have resolved before Screening
- Resolved medical/ophthalmic conditions that are deemed relevant by the investigator
- Relevant surgeries/procedures

Throughout the subject's participation, obtain information on any changes in medical health. Medical history will be collected in the eCRF as outlined in the MOP.

9.1.4 Prior and Concomitant Medication Assessments

Any medication (including vaccines, OTC or prescription medicines, vitamins, and/or herbal supplements) will be queried and recorded on the appropriate case report form and updated at each visit. Prior medications taken up to 30 days prior to the Screening must also be recorded.

Concomitant medications will be collected in the eCRF as outlined in the MOP.

9.1.5 Urine Pregnancy Test

Women who are pregnant or breastfeeding are excluded from participation in the study. A urine pregnancy test will be performed at Visit 1/Screening, Visit 4/Exit, Early Exit, and Unscheduled Visits (as necessary) in all females of childbearing potential.

9.2 Efficacy Assessments and Procedures

9.2.1 IDEEL-SB Questionnaire

IDEEL-SB Questionnaire score will be completed by the subject at Visit 1/Screening and Visit 4/Exit Day 30 ± 5/Early Exit.

9.3 Safety Assessments and Procedures

9.3.1 Adverse Event Collection

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

9.3.2 Device Deficiency Collection

Assess and record any device deficiencies that are observed or reported since the previous visit.

9.3.3 Slit Lamp Biomicroscopy

SLE of the cornea, conjunctiva, eyelids, and ocular surface must be performed in both eyes.

9.3.4 Best Corrected Visual Acuity

LogMAR visual acuity using the ETDRS and/or SOC chart for both eyes must be performed.

9.3.5 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 non-study personnel, the investigator is to capture adverse event-related information on the adverse event form upon becoming aware.

If a subject experiences any symptoms of eye infections, including but not limited to eye pain, eye redness, eye irritation, they need to schedule an Unscheduled Visit and seek medical advice or treatment.

During an Unscheduled Visit (for an adverse event), the investigator must conduct the following procedures:

- Collect adverse event and device deficiencies information
- Record changes in medical condition or concomitant medication
- Perform BCVA
- Perform slit lamp biomicroscopy exam

The investigator may perform additional procedures for proper diagnosis and treatment of the subject. The investigator must document this information in the subjects' 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 2-2, as possible.

Spare IP is not dispensed to the subject in this study. If IP is lost, damaged, or needs to be replaced due to an AE/device deficiency, the subject will be instructed to return for an unplanned dispense visit. Refer to the MOP for more details.

9.4 Adverse Events and Serious Adverse Events

9.4.1 Definitions of AE and SAE

The following definitions of terms apply to this section:

- Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- Adverse drug reaction (ADR): All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs. Responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Adverse Event of Special Interest (AESI): Adverse event (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
- Life-threatening AE or life-threatening ADR: an AE or ADR is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or ADR that, had it occurred in a more severe form, might have caused death.
- Serious adverse event (SAE) or serious adverse reaction (SAR): an AE or AR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:
    - Death, a life-threatening or sight-threatening AE,

- a subject hospitalization or prolongation of existing hospitalization, Note: Planned hospitalization for a preexisting condition, without serious deterioration in health, is not considered a serious adverse event. Therefore, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as a serious adverse event when the hospitalization or prolonged hospitalization was for an elective surgical procedure or for a preexisting condition. 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.
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (disability), or
- a congenital anomaly/birth defect
- Important medical event or reaction that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

Note: Medical and scientific judgment should be exercised in deciding whether other situations should be considered as serious such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected unexpected SAR (SUSAR): Adverse drug reaction that is both unexpected and meets the definition of a serious adverse event.
- Unexpected AE or unexpected ADR: an AE or ADR is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

9.4.2 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs should be documented from the time the subject provides informed consent until subject participation in the trial has been completed.

9.4.3 Identifying AEs and SAEs

AE information may be volunteered by the subject or solicited by trial personnel through non-leading questions. 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?"

AEs should be reported for any clinically relevant change, as determined by the investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

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 [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.

9.4.4 Recording of AEs and SAEs

All AEs occurring during the trial, regardless of the assumption of causal relationship, must be documented on the respective CRF. Qualified trial staff responsible for assessing AEs will be listed on the Site Authorization and Delegation Log. This includes assessment of AE severity and relationship to treatment.

Documentation of AEs/ARs will include AE description, start date and stop date, severity, relationship, action(s) taken, seriousness, and outcome.

When recording an AE, the following information should be provided on the trial AE CRF:

Action taken with trial intervention:

- None
- Trial intervention discontinued
- Trial intervention interrupted

AE outcome:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown/lost to follow-up

Further details on assessing severity and causality of AEs and SAEs are in Appendix 14.

9.4.5 Follow-up of AEs and SAEs

If an AE/SAE is unresolved at the time of exit, efforts will be made to follow up until the AE/SAE is resolved or stabilized, the subject is lost to follow-up, or there is other resolution to the event. These follow-up visits will be documented.

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 study treatment. 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 within 30 days after subject has stopped study participation (last visit or time of last dose of the study treatment taken (whichever is later) must be documented and available upon the study sponsor's request.

9.4.6 Reporting of SAEs

An investigator must immediately (i.e., within 24 hrs) report any SAE or SAR to the sponsor or sponsor representative, whether or not considered trial intervention-related, including those listed in the protocol or IB. The investigator must use the SAE report form (eCRF or email as a back-up) and include an assessment of whether there is a reasonable possibility that the trial intervention caused the event. The investigator must report any SAE or SAR that occurs or is observed during the trial. In case of incomplete information, the investigator must provide follow-up information as soon as possible, again using the SAE report form. The details for SAE/SAR report submission are listed below.

Report SAEs/SARs within 24 hrs via electronic data capture (EDC) system or, in the case of the EDC system not being available, the provided SAE source document will be completed and sent via the instructions noted on the form to the sponsor representative within the expected reporting time frame.

SAE/SAR reports will be evaluated by the medical monitor. Regulatory authorities, IRB/IEC, and investigators at each of the trial sites will be informed as required.

An assessment of seriousness will also be performed for all adverse events by a sponsor physician utilizing the same criteria. If an adverse event reported for an investigator's subject is upgraded to a serious adverse event by a sponsor physician, the investigator will receive a notification from the sponsor.

9.4.7 Regulatory Reporting Requirements for SAEs

This clinical study is being conducted exclusively in the US where the IP is considered an OTC monograph drug. As such, there are no regulatory requirements to report SAEs to the health authority. There are no IRB requirements for an OTC monograph drug.

9.4.8 Serious and Unexpected Adverse Reaction Reporting

An investigator must immediately (i.e., within 24 hrs) report SUSARs. In the event of SUSAR, the site must notify the medical monitor for the trial and submit an SAE report form in EDC within 24 hrs of notification, observation, or occurrence of the SUSAR, whether or not complete information is available to the sponsor or sponsor representative. In the case of

incomplete information, the investigator must provide follow-up information as soon as possible using the SAE report form.

9.4.9 Adverse Events of Special Interest

Not applicable to this study.

9.4.10 Disease-related Events or Outcomes Not Qualifying as AEs or SAEs

Any medical condition present prior to informed consent which remains unchanged or improved should not be recorded as an AE at subsequent visits. However, an AE should be recorded if the frequency, intensity, or the character of a preexisting condition worsens during the trial period beyond what would be expected from the natural progression of that condition.

Surgery should not be reported as an adverse event nor as an outcome of an adverse event if the purpose of the surgery was diagnostic and the outcome was uneventful.

If there is a question as to whether a medical development should be reported as an adverse event, it is recommended the investigator contact the sponsor for guidance.

9.5 Device Deficiencies

A device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer. A device deficiency may or may not be associated with patient harm (i.e., AE or SAE); however, not all AEs or SAEs 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:

- Defective component
- Damaged package
- Mixed/mislabeled
- Potential contaminant
- Tampered seal
- Incorrect capping

- Partial seal
- Other (specify)

9.6 Pregnancy and Postpartum Information

Pregnancies occurring in subjects enrolled in the study must be reported and followed to outcome. No further study treatments will be administered to pregnant subjects; however, the subject will be encouraged to complete all visits in the study.

If a woman is of childbearing potential, she must have a pregnancy test performed at the Screening and/or Baseline visits prior to confirmation of eligibility (and prior to start of study treatment). Additional pregnancy tests may also be required per local regulatory guidelines. Subjects with a positive pregnancy test result must be excluded from the study. Subjects with a negative pregnancy test result must agree to use a highly effective contraception method during the study.

While pregnancy itself is not considered to be an AE, pregnancy reports are tracked by the sponsor or sponsor representative. The investigator must complete the Pregnancy Report Form and email or fax the form to the sponsor or sponsor representative. Following delivery or termination of the pregnancy, the Pregnancy Report Form is to be completed and sent by email or fax to the sponsor or sponsor representative.

Premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as a serious adverse event (SAE). Other pregnancy complications should be reported as SAEs if they meet the seriousness criteria. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE must be submitted for the child. Furthermore, all neonatal deaths that occur within 30 days of birth, without regard to causality, should be reported as SAEs.

9.7 Device Deficiencies for Drug/Device Combination Products

N/A

9.8 Pharmacokinetics

N/A

9.9 Genetics

N/A

9.10 Biomarkers

N/A

9.11 Immunogenicity Assessments

N/A

9.12 Medical Resource Utilization and Health Economics

N/A

10 STATISTICAL CONSIDERATIONS

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

Unless otherwise specified, baseline will be defined as the last available measurement prior to IP exposure. Change from baseline will be calculated as postbaseline timepoint/visit value minus baseline value.

Final subject evaluability must be determined prior to locking the database, based upon the data evaluability plan (DEP).

The primary analysis will be conducted on the Safety Analysis Set (Section 10.1) at Day 30, for the change from baseline calculation.

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.

10.1 Analysis Set

Two analysis data sets will be defined.

Safety Analysis Set: includes all subjects/eyes exposed to at least one dose of IP.

Per Protocol (PP) Analysis Set: is a subset of the Safety Analysis Set and excludes all data meeting any of the critical deviation or evaluability criteria specified in the DEP.

10.2 Analyses Supporting Primary Objective(s)

[redacted]

The Safety Analysis Set will serve as the primary analysis set for the primary efficacy endpoint.[redacted]

[redacted]

10.2.1 Statistical Model, Hypothesis, and Method of Analysis

The null and alternative hypotheses for the analysis of the primary efficacy endpoint are:

H_0: $\mu_{(T)} \geq 0$

H_a: $\mu_{(T)} < 0$

where $\mu_{(T)}$ denotes the mean change from baseline in total IDEEL-SB score at Day 30.

A paired (one-sample) t-test will be used on the change from baseline value at Day 30 to test these hypotheses. One-sided p-value will be calculated, and null hypothesis will be rejected if p-value < 0.05.

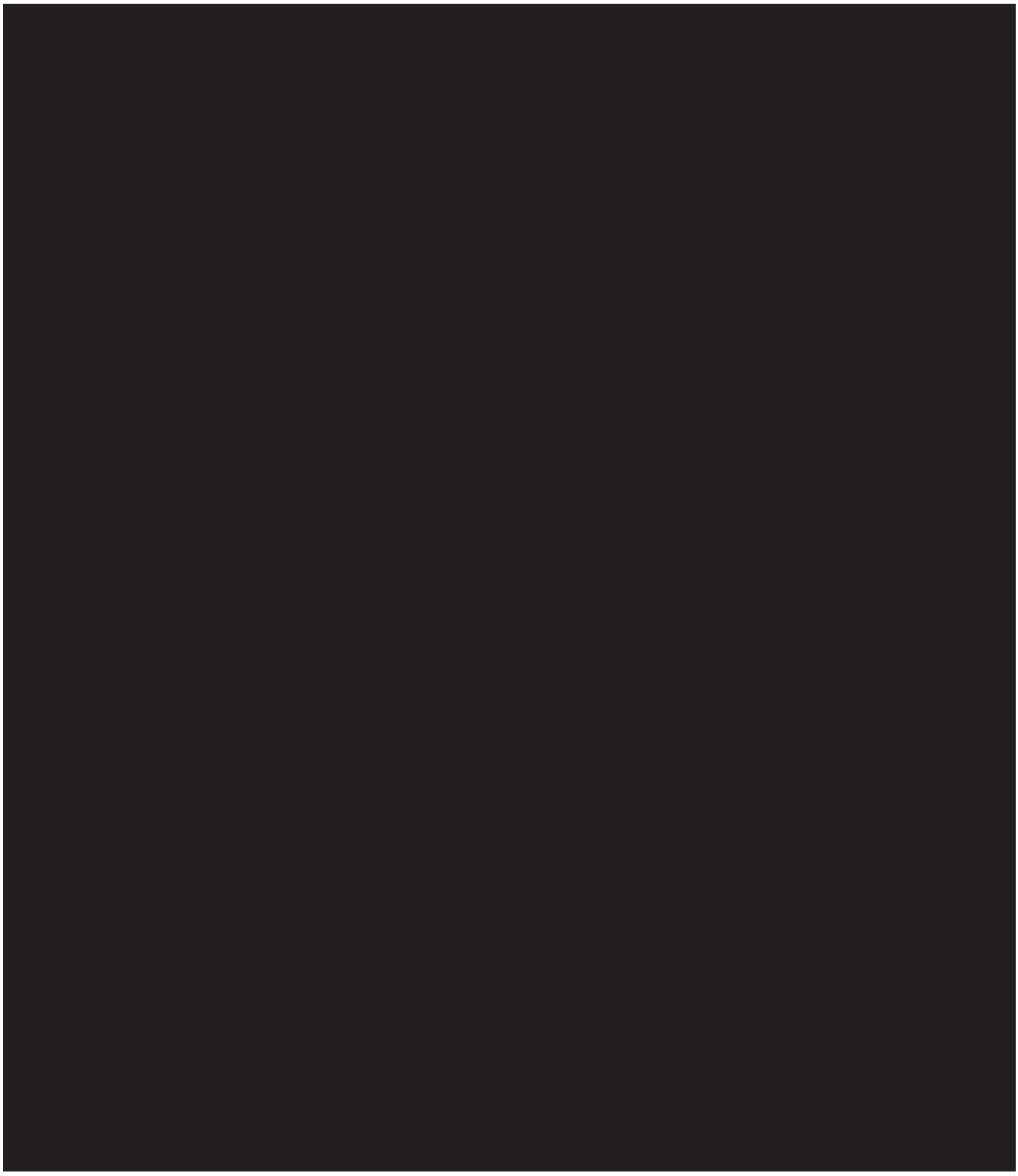
In addition, descriptive statistics for observed and change from baseline values will be summarized.

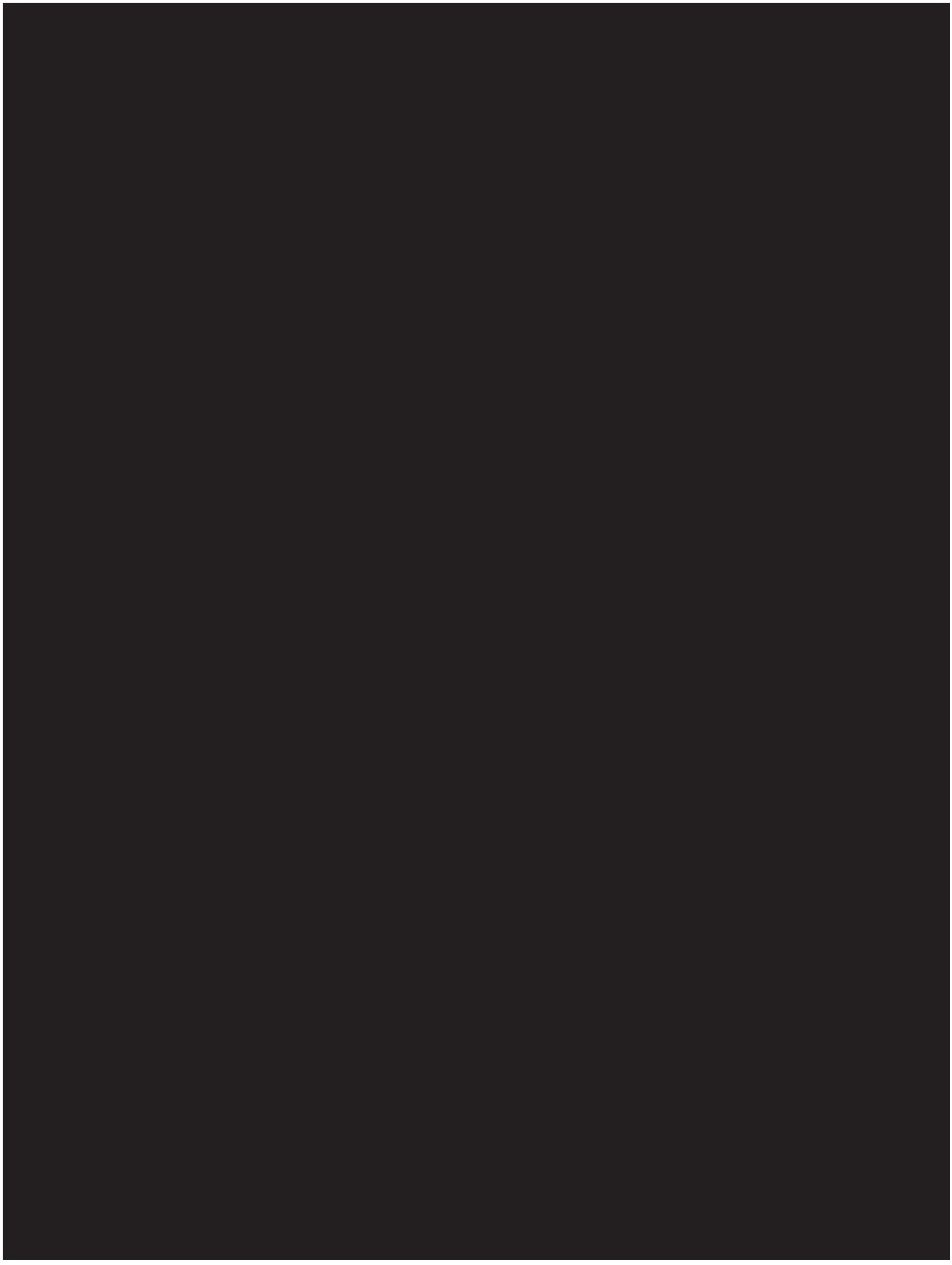
10.2.2 Handling of Intercurrent Events of Primary Estimand(s)

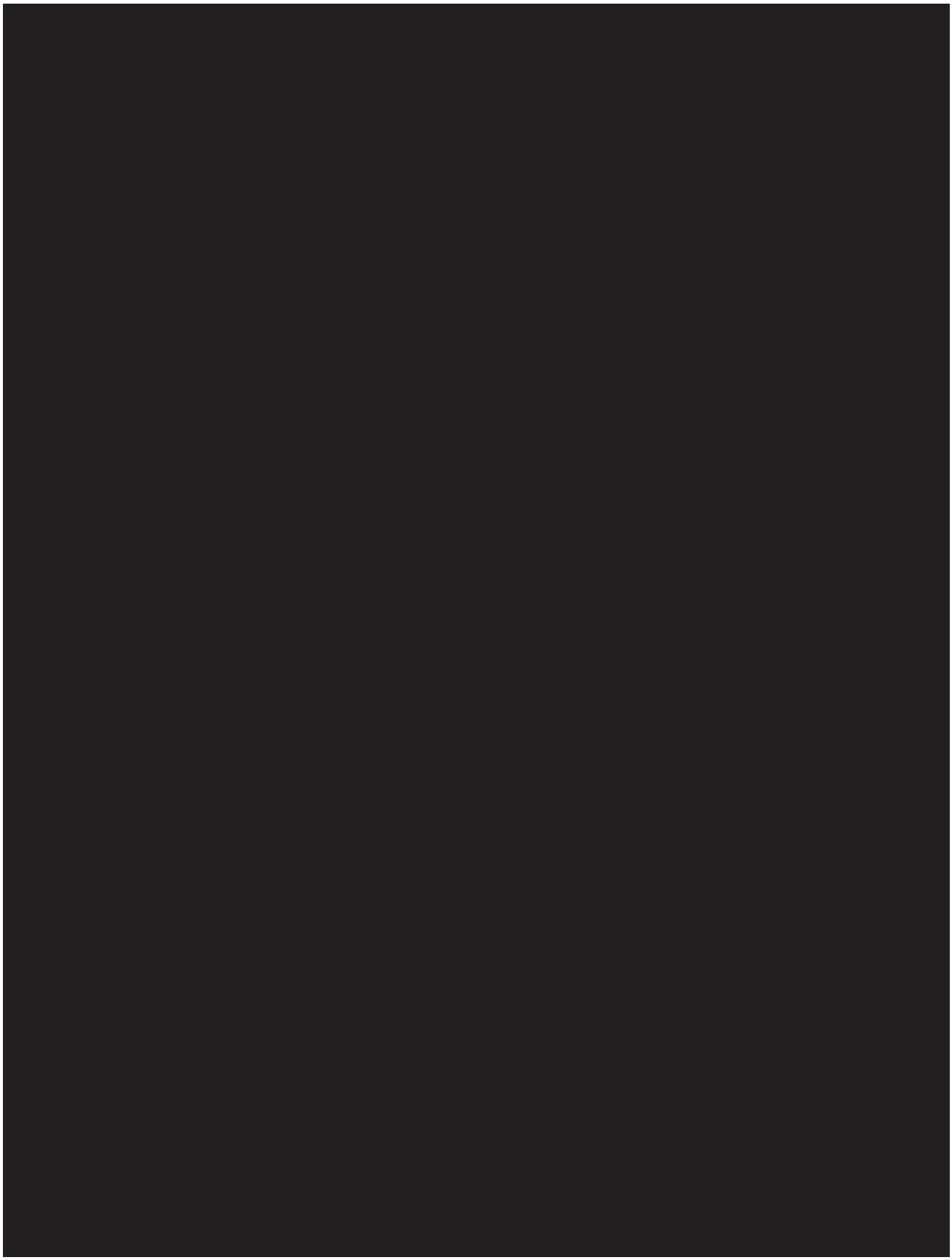
The treatment-policy strategy will be used whereby all subjects exposed to at least one dose of IP, regardless of any ICE, will be included in the analysis. In addition, should an ICE result in a protocol deviation, data evaluability will be determined prior to final database lock and analysis will also be done on a per-protocol basis, as applicable.

10.2.3 Handling of Missing Data Not Related to Intercurrent Events

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 efficacy analysis.







10.5 Safety Analyses

The safety endpoints are

- AEs
- BCVA
- Biomicroscopy findings
- Device deficiencies

There are no safety hypotheses planned in this trial. 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 day of first exposure to IP.

Each biomicroscopy parameter will be summarized. For lens and status of lens biomicroscopy parameter, counts and percentages of eyes that experience an increase of ≥ 1 grade from baseline (last assessment prior to study product exposure) to any subsequent visit will be presented; all other parameters counts and percentages of eyes that experience an increase of ≥ 2 grades from baseline (last assessment prior to study product exposure) to any subsequent visit will be presented. A supportive listing will be generated which will include all biomicroscopy data from all visits for those eyes experiencing the increase.

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

No inferential testing will be done for safety analyses.

[redacted]

[redacted]

11 PROTOCOL DEVIATIONS

Per ICH E6 (GCP) R2 Section 4.5.1 the investigator/institution should conduct the study in compliance with the protocol agreed with the sponsor and, if required, by the regulatory authority and which was given approval/favorable opinion by IRB/IEC.

Protocol waivers or deviations from the protocol inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study regulatory acceptability or Subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The site will contact the sponsor for clarification of inclusion and/or exclusion criteria as needed prior to enrollment of the study subject. The sponsor or their representative will document clarification requests and responses. If a Subject does not meet any of the eligibility criteria, that Subject may not be enrolled into the study.

If the investigator feels that in his/her clinical judgment, it is necessary to promptly implement reasonable alternatives to, or deviations from, the protocol in consideration of the safety of study subjects, the sponsor is to be notified of these alternatives and deviations, and the reasons for such changes are to be documented in the study records. The investigator is to also notify his/her IRB/IEC of any such changes.

If a significant protocol deviation is identified by the investigator or through site monitoring activities, an immediate submission to the IRB/IEC may be required (as per IRB/IEC guidelines). The sponsor will assess any protocol deviation and decide whether any of these non compliance should be reported to the relevant competent authority as a serious breach of Good Clinical Practice (GCP) and the protocol. If per the relevant competent authorities' requirements, the protocol deviation is not required to be reported immediately but is still required to be notified to the IRB/IEC, the specific protocol deviation will be added to the annual progress report.

The sponsor will review, designate, and/or approve all protocol deviations prior to the database lock.

12 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND STUDY OVERSIGHT

12.1 Regulatory and Ethical Considerations

The study will be conducted according to this clinical protocol and will be governed by all applicable governmental rules and regulations concerning the conduct of clinical trials on human subjects. This includes, but is not limited to:

- The approval of IRB/IEC
- The Helsinki Declaration (World Medical Association 2013)
- US Code of Federal Regulations, Title 21
- International Conference on Harmonisation (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- Standard operating procedures of the sponsor and any other vendors participating in the conduct of the trial
- EU Clinical Trials Regulation 536/2014 and EC local laws and regulations
- Obtaining prospective informed consent

The investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. The investigator is not allowed to deviate from the protocol except to protect the rights, safety, and wellbeing of human subjects under emergency circumstances. Emergency deviations may proceed without prior approval of the sponsor and the IRB/EC but shall be documented and reported to the sponsor and the IRB/EC as soon as possible. Deviations from this protocol, regulatory requirements, and/or GCP must be recorded and reported to the sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Failure to implement identified corrective and preventative actions may result in site closure by the sponsor. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the ICF, 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), ICF, 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 IFU and IB, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. Any additional requirements imposed by the EC or regulatory authority shall be followed. At the end of the study, the investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

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

The investigator must have a defined process in case a subject would like to withdraw their consent (s). The investigator is the designated contact point for any such withdrawals.

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

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

12.2 Committees

N/A

12.3 Informed Consent Process

Prior to any study procedures, the study will be discussed with each subject and subjects wishing to participate must give written informed consent including appropriate privacy authorization, as applicable. The verbal explanation of the study will cover all the elements specified in the written information provided for the subject. The investigator will inform the subject of the aims, methods, anticipated benefits, and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and, if necessary, may ask for more information. At the end of the interview, the subject should be given time to reflect. The subjects and/or legally authorized representative then will be required to sign and date the ICF. Consent procedures

must follow local legal requirements of the study site. A copy of the signed and dated consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the trial files at the investigator's site.

The investigator or staff is responsible for ensuring that no subject undergoes any study related examination or activity before the subject has given written informed consent. It should be emphasized that the subject is at liberty to withdraw consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study and should be notified that discontinuation from the study will not impact their subsequent care.

If the subject is part of a vulnerable population, including without limitation minors, or requires any special needs, ensure that a parent or legal guardian signs the informed consent and that the subject signs an IRB/IEC-approved assent document as required.

12.4 Privacy and Data Protection

The investigator must ensure that the subject's identity is kept confidential throughout the course of the study. In particular, the investigator must maintain appropriate safeguards to prevent unauthorized use or disclosure of, or access to, subject data, and keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study subject. The study sponsor may collect a copy of the enrollment log without any directly identifying subject information.

The study sponsor may share subject-level data collected in this study 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.

12.5 Early Site Closure or 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. The investigator may terminate the site's participation in the study for reasonable cause.

If the clinical study is prematurely terminated or suspended:

- 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.

13 GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

13.1 Quality Tolerance Limits

Quality tolerance limits (QTLs) will be predefined through an internal risk management process and monitored on an ongoing basis, with documentation of QTLs that are met summarized in the CSR.

13.2 Data Quality Assurance

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.

13.3 Source Data

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.

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.

14 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

14.1 Severity

Severity of an AE is defined as a qualitative assessment of the level of discomfort or the degree of intensity of an AE as determined by the investigator or reported to them by the subject. The assessment of severity is made irrespective of trial medication relationship or seriousness of the event and should be evaluated according to the following scale:

- 1 = Mild: present and noticeable, but not distressing, and no disruption of normal daily activities
- 2 = Moderate: bothersome, discomfort sufficient to possibly reduce or affect normal daily activity
- 3 = Severe: incapacitating, with inability to work or perform normal daily activity

A change in increased severity for a reported AE will require a stop date for the previous severity and a new start and stop date for the new severity. E.g., a change in severity may go from mild to moderate, or from moderate to severe. In either case, the start and stop dates should be recorded.

Note: A severe AE is not the same as a serious AE. Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations, if applicable.

14.2 Causality

Relationship between the AE and the trial intervention or trial procedure will be determined by the investigator, as applicable, for each AE using these explanations:

- Not Related: The event is clearly related to other factors such as subject's clinical condition, therapeutic interventions, concomitant disease, or therapy administered to the subject and does not follow a known response pattern to the product, device, or procedure.

- Related: The event follows a reasonable, temporal sequence from the time of trial medication administration or trial procedure and/or follows a known response pattern to the product, device or procedure and cannot be reasonably explained by other factors such as subject's clinical state, therapeutic interventions or concomitant therapy administered to the subject, and either occurs immediately following trial medication administration or procedure, or improves on stopping the trial medication, or reappears on repeat exposure, or there is a positive reaction at the application site.

14.3 Expectedness

AEs or ARs are considered "unexpected" if they are not listed in the reference safety information section of the IB for (trial intervention) or are not listed at the specificity or severity that has been observed. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB as occurring with this class of drugs or as anticipated from the pharmacological properties of (trial intervention) and are not specifically mentioned as occurring with the trial drug.

E.g., under this definition, glaucoma would be unexpected (by virtue of greater severity/specificity) if the IB referred only to elevated intraocular pressure.

An investigator must immediately (i.e., within 24 hrs from time of awareness) report any SAE or SAR to the sponsor or its CRO representative, whether or not considered drug-related, including those listed in the protocol or IB.

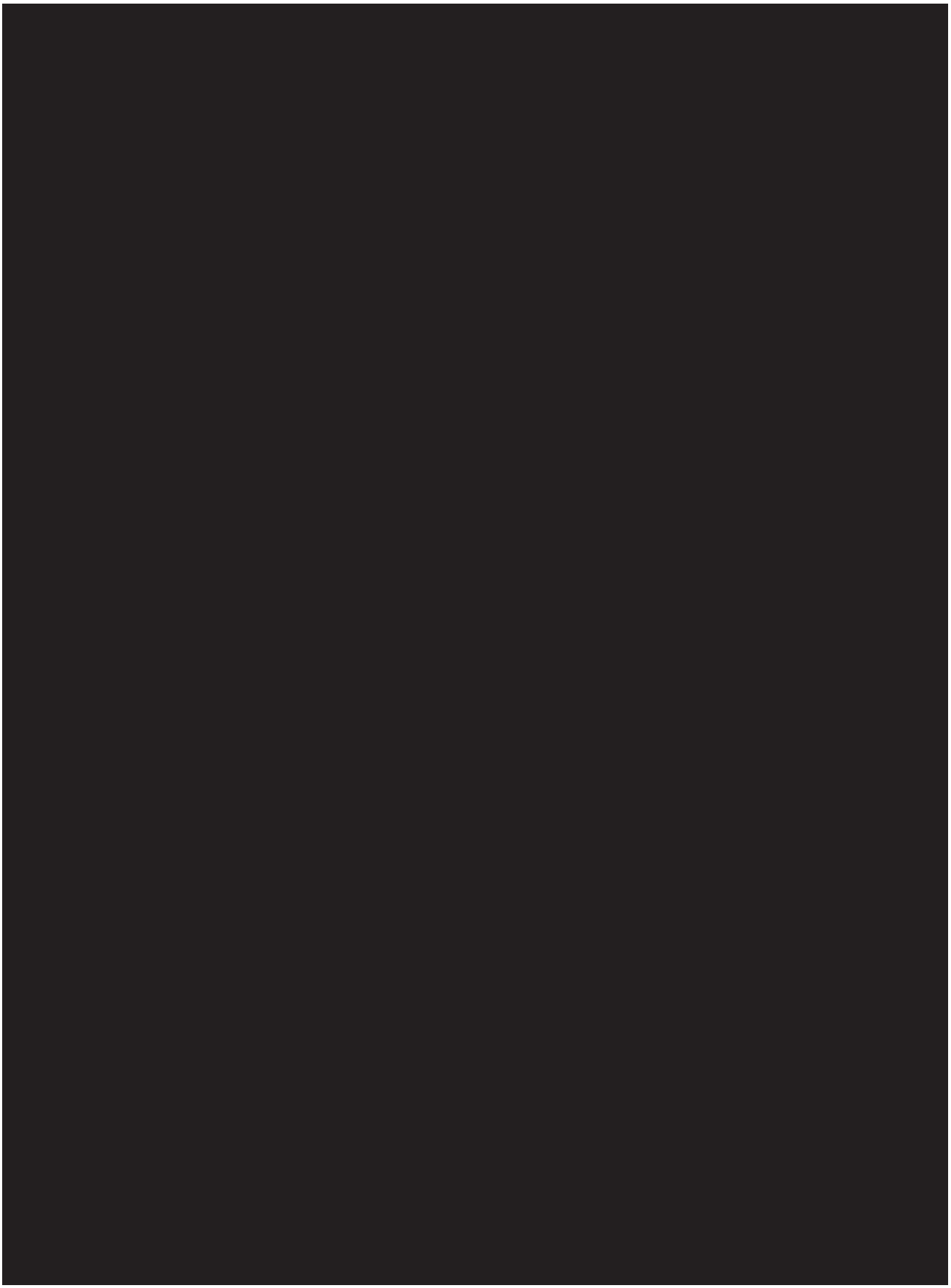
15 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

15.1 Contraception and Pregnancy Testings

Urine pregnancy testing will be performed in women of childbearing potential at Visit 1/Screening and Visit 4/Exit.

15.2 Country/Region-Specific Differences

N/A



16 PUBLICATIONS

There are no immediate plans to submit the results of this phase 3 study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing.

17 REFERENCES

17.1.1 Internal References

- Manual of procedures
- Investigator brochure
- Instructions for use

17.1.2 External 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 54 - Financial Disclosure by Clinical Investigators
- The Helsinki Declaration (World Medical Association 2013)
- US Code of Federal Regulations, Title 21
- International Conference on Harmonization (ICH) Consolidated Good Clinical Practice Guideline (E6 R2)
- EU Clinical Trials Regulation 536/2014 and EC local laws and regulations
- EN ISO 14155:2020&LC:2020 Clinical investigation of medical devices for human subjects. Good clinical practice.

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