A Phase 3b Study to Evaluate 0.003% AR-15512 Safety and Drop Attributes

STUDY ID

DEF512-E005

PROTOCOL v.2

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Clinical Trial Protocol: DEF512-E005

Protocol Title:	A Phase 3b Study to Evaluate 0.003% AR-15512 Safety and Drop Attributes
Protocol Number:	DEF512-E005
Study Phase:	Phase 3b
Investigational Product Name:	AR-15512 ophthalmic solution 0.003%
IND Number:	147005
Indication:	Dry Eye Disease
Investigators:	Multi-Center
Sponsor:	Alcon Research, LLC and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099
Contract Research Organization:	Ora, Inc. 138 Haverhill Street Suite 102 Andover, MA 01810, U.S.A Phone: +1-978-685-8900

CONFIDENTIAL STATEMENT

1 SYNOPSIS

Protocol Title:	A Phase 3b Study to Evaluate 0.003% AR-15512 Safety and Drop Attributes
Protocol Number:	DEF512-E005
Investigational Product:	AR-15512 ophthalmic solution 0.003%
Study Phase:	Phase 3b
Primary Objective(s):	To evaluate the proportion of ocular adverse events reported in subjects with dry eye disease (DED) between the intervention arm [0.003% AR-15512 (512)] vs. Refresh® Classic.
[redacted]	
Overall Study Design:	
Structure:	Multi-center, subject-masked, randomized, single-visit, crossover study
Duration:	This study will consist of a 1 day single visit (acute), lasting approximately 7-8 hours.
Dosage/Dose Regimen/ Instillation/Application/Use:	Qualified subjects will be dosed once with an artificial tear (Refresh Classic), as 1 drop in the **right eye only**, by site staff prior to instillation of any variation of 512. After a wait period of 30 minutes ± 5 minutes, subjects will then receive 512, instilled in clinic by site staff. **Note:** Four 512 instillation variations will be utilized (in randomized sequence starting with the left eye). A wait period of 30 minutes ± 5 minutes will take place between left eye and right eye instillation. Each variation will be instilled in only 1 eye. Following the first two instillation variations, a wait period of 2 to 3 hours must elapse prior to instillation of the remaining two 512 variations.
Summary of Visit Schedule:	The study consists of 1 Visit (Screening, Enrollment and Assessments).
Study Population Characteristics:	
Number of Subjects:	Approximately 36 to 55 subjects will be enrolled.
Condition/Disease:	Dry Eye Disease

Inclusion Criteria:	To be eligible to participate in this trial, an individual must meet all the following criteria: 1. Male or female, 18 years of age or older. [redacted] 3. Corrected Visual Acuity (Snellen) 20/200 or better in both eyes. 4. Good general and ocular health, as determined by the Investigator using medical history, ophthalmic examination and history. 5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. 6. Written informed consent from the subject has been obtained prior to any study-related procedures. 7. Able, as assessed by the Investigator, and willing to follow study instructions.
Exclusion Criteria:	Subjects meeting any of the following criteria will be excluded from entry into the study: <u>Ophthalmic:</u> 1. Current evidence of other clinically significant ophthalmic disease other than dry eye (e.g., glaucoma or macular degeneration). **Note:** Blepharitis and/or Meibomian gland disease not requiring treatment are allowed. 2. Use of artificial tears within 2 hours of the Study Visit. 3. History of ocular surgery within 1 year of the Study Visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision). 4. Current evidence of other significant ophthalmic disease requiring topical medication (e.g., glaucoma, ocular hypertension) or other ophthalmic disease which the Investigator believes may interfere with study findings or interpretation. 5. History of corneal transplant in one or both eyes. 6. Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex

	or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease. 7. Use of contact lenses in either eye within 7 days of the Study Visit. 8. Punctal or intracanalicular plug present in either eyelid within 14 days of the Study Visit. 9. Use of regular lid hygiene (all forms of lid care including lid wipes, scrubs and purposeful cleansing of lids with soap or medicated shampoos, etc.) or heat masks within 7 days of the Study Visit. 10. Use of lid heating therapy (i.e., LipiFlow®, iLUX®, TearCare®) or Meibomian gland probing/therapeutic expression within 3 months of the Study Visit. 11. Use of Intense Pulsed Light therapy on eyelids within 3 months of the Study Visit. 12. Use of any topical ocular anti-inflammatory medications (e.g., ocular cyclosporine [Restasis®, Cequa™, Vevye™, generics], lifitegrast [Xiidra®]) or any other prescription ophthalmic product for DED (e.g., perfluorohexyloctane [Meibo™]), any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days of the Study Visit. 13. Use of topical ocular autologous serum within 30 days of the Study Visit. 14. Use of any other topical ocular drop (prescription or OTC, including artificial tears) within 2 hours of the Study Visit. 15. Use of Tyrvaya™ (varenicline solution, nasal spray 0.03mg) within 30 days of the Study Visit. 16. Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days of the Study Visit. <u>General/Systemic:</u> 17. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) within 7 days of the Study Visit. 18. Initiation, discontinuation, or change in dose of a systemic corticosteroid within 14 days of the Study Visit. **Note:** Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) are not applicable to this exclusion.

	19. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) within 30 days of the Study Visit. 20. Vaccination within 3 days prior to the Study Visit. 21. Use of an investigational product or device within 30 days of the Study Visit. 22. At the Study Visit, at the Investigator's discretion, have uncontrolled or severe: a. Systemic allergy b. Rhinitis or sinusitis 23. History or presence of significant systemic disease (i.e., cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic). Significant is defined as any disease that, in the assessment of the Investigator, would put the safety of the subject at risk through participation, or would prevent or confound protocol-specified assessments (e.g., severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.). 24. Known allergies or sensitivity to the study interventions or study diagnostic agents. 25. Positive pregnancy test or currently breastfeeding. 26. The subject has a condition or is in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
Study Formulations:	• AR-15512 ophthalmic solution 0.003% • Refresh Classic
Evaluation Criteria:	
Primary Endpoint:	• Proportion of ocular AEs reported by intervention arm (512 vs. Refresh Classic).

[redacted]

[redacted]

Safety Measures:	• Corrected Visual Acuity • Slit-Lamp Biomicroscopy • Adverse Events (AEs)

General Statistical Methods and Types of Analyses

Analysis Sets:

- Safety Analysis Set (SAF): The SAF will include all subjects who have received at least one dose of Refresh Classic or one dose of 512.
- Full Analysis Set (FAS): The FAS will include all subjects who have received at least one dose of Refresh Classic and one dose of 512 instillation variation, and who have at least one rating of the Rating Sensation Assessment.

[redacted]

Safety Analysis:

The AEs will be collected after subject signs the ICF and coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version. Treatment-emergent adverse events (TEAEs) will be summarized using the SAF by system organ class and preferred term. Other safety parameters collected will be summarized.

Sample Size Determination:

No power calculation will be used to determine the sample size. [redacted] The study aims to recruit approximately 36 to 55 subjects.

Summary of Known and Potential Risks and Benefits to Human Subjects

512 is a Transient Receptor Potential Melastatin 8 receptor agonist. 512 (FL-no. 16.123) has been used as a flavoring agent or adjuvant in the food industry for many years and is generally recognized as safe for these purposes (USFDA/FEMA GRAS No. 4681) in or on human food products with no safety concerns at specified use levels (EU/EFSA 2014; WHO/JECFA No. 2079).

Based on available information including that from the completed 512 non-clinical development program, data support that when delivered BID through topical ocular administration, 512 possesses the appropriate pharmacologic profile with an acceptable margin-of-exposure (i.e., wide therapeutic index) to fully support the safe use of 512.

[redacted]

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
BID	Twice Daily
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Clinical Research Organization
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
GCP	Good Clinical Practice
GRAS	Generally Recognized as Safe
HR	Hazard Ratios
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
LogMAR	Logarithmic Minimum Angle of Resolution
LS Means	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
[redacted]	[redacted]
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-Emergent Adverse Event
TRPM8	Transient Receptor Potential Melastatin 8
WOCBP	Women of Childbearing Potential

4 INTRODUCTION

4.1 Dry Eye Disease

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Craig 2017).

Despite the availability of several pharmaceutical products, there remains a significant unmet need for an effective topical ocular therapeutic to effectively treat the signs and symptoms of DED.

In recent years, increased attention has been placed on the neuronal regulation of tear production. AR-15512 is a potent and selective agonist of Transient Receptor Potential Melastatin 8 (TRPM8) that is being developed for the treatment of the signs and symptoms of DED. When applied topically to the eye, AR-15512 activates cold thermoreceptor nerve terminals of the cornea leading to regulation of tear production and blink rate. In addition, a cooling sensation may be produced that could be beneficial for reduction of ocular discomfort. Preclinical and clinical evidence to date support the mechanism of AR-15512 as an agonist of TRPM8 and the ability of AR-15512 to modulate corneal nerve impulse activity leading to increased tear production and a reduction of DED symptoms.

5 STUDY OBJECTIVES

5.1 Primary Objective(s)

- To evaluate the proportion of ocular adverse events reported in subjects with DED between the intervention arm (512) vs. Refresh Classic.

6 CLINICAL HYPOTHESES

The clinical hypothesis for this study is that adjustments in 512 instillation procedure will reduce either the intensity or duration of subject reported instillation site sensation.

7 OVERALL STUDY DESIGN

This is a Phase 3b, subject-masked, randomized, single-visit, crossover design conducted in the United States at approximately 6 sites.

Approximately 36 to 55 DED subjects will be enrolled. The study will consist of 1 Visit (Screening, Enrollment, Assessments). All subjects will be exited from the study at the end of the Study Visit.

At the end of the Screening phase, all qualified subjects will be enrolled and instilled a drop of artificial tear (Refresh Classic) in the **right eye only**. All subjects will then be dosed with 512 under four different instillation variations as described in Table 1. Subjects will be randomized to one of the four sequences of 512 instillation variations based on a Williams design randomization sequence (Table 2).

Each 512 instillation variation will be dosed in one (**1) eye only** as described in the randomization sequence (Table 2), starting with the **left eye**. After the first two 512 instillation variations are complete, subjects will start a wait period of a minimum of 2 hours and a maximum of 3 hours prior to completion of dosing of the remaining two 512 instillation variations. A wait period of 30 minutes ± 5 minutes will take place between left eye and right eye instillation. [redacted]

Details of assessments performed can be found in Appendix 1 (Schedule of Procedures) as well as in the Manual of Procedures.

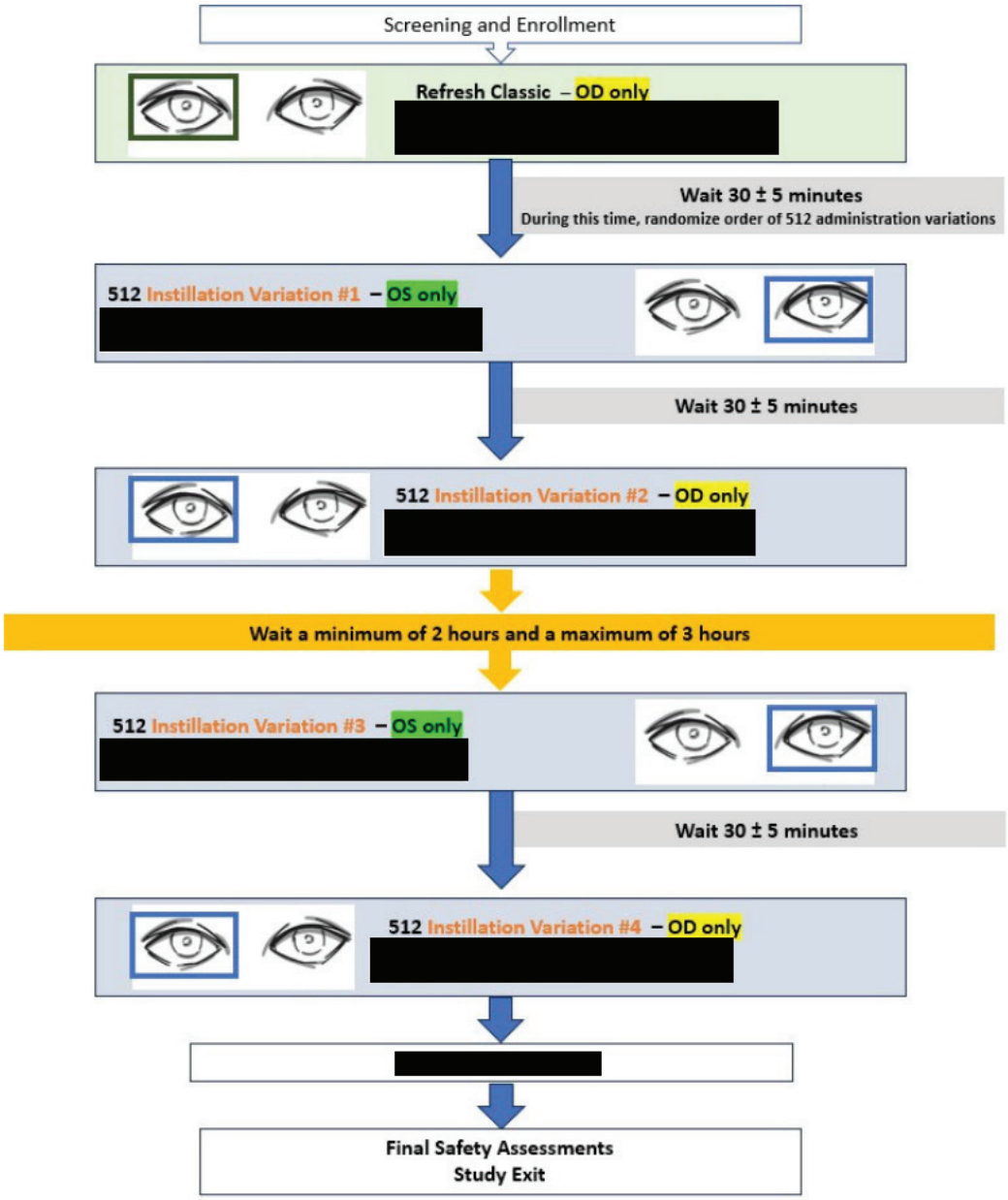
Table 1 Summary of 0.003% AR-15512 Instillation Variations

Instillation Variation Name	Instillation Variation Description
512-RT (base case)	0.003% AR-15512 instilled at room temperature, eyes to remain open post-drop instillation.
512-COLD	0.003% AR-15512 stored in refrigerator [redacted] and instilled immediately [redacted] after removal from refrigerator, eyes to remain open post-drop instillation.
512-RT-EC	0.003% AR-15512 instilled at room temperature followed by subjects immediately closing their eyes [redacted]
512-COLD-EC	0.003% AR-15512 stored in refrigerator [redacted] and instilled immediately [redacted] post removal from refrigerator followed by subjects immediately closing their eyes [redacted]

Table 2 Randomization Sequences Using a Williams Design for 0.003% AR-15512 Instillation Variations

Sequence	Period			
	1	2	3	4
1	512-RT	512-COLD	512-RT-EC	512-COLD-EC
2	512-RT-EC	512-RT	512-COLD-EC	512-COLD
3	512-COLD	512-COLD-EC	512-RT	512-RT-EC
4	512-COLD-EC	512-RT-EC	512-COLD	512-RT

Figure 1 Study Design Diagram



Abbreviations: min = minutes; OD = right eye, OS = left eye

8 STUDY POPULATION

8.1 Number of Subjects

This study is anticipated to enroll approximately 36 to 55 subjects with DED. To achieve this goal, approximately 70 subjects may be screened.

8.2 Study Population Characteristics

All subjects must be at least 18 years of age, of either sex at birth, and of any race, and must meet all inclusion criteria and none of the exclusion criteria.

8.3 Inclusion Criteria

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female, 18 years of age or older.

3. Corrected Visual Acuity (Snellen) 20/200 or better in both eyes.

4. Good general and ocular health, as determined by the Investigator using medical history, ophthalmic examination and history.

5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6. Written informed consent from the subject has been obtained prior to any study-related procedures.

7. Able, as assessed by the Investigator, and willing to follow study instructions.

8.4 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from entry into the study:

<u>Ophthalmic:</u>

1. Current evidence of clinically significant ophthalmic disease other than DED (e.g., glaucoma or macular degeneration).
   Note: Blepharitis and/or Meibomian gland disease not requiring treatment are allowed.

2. Use of artificial tears within 2 hours of the Study Visit.

3. History of ocular surgery within 1 year of the Study Visit, including punctal cautery, corneal refractive, or anterior segment surgeries that affect corneal sensitivity (e.g., cataract surgery or any surgery involving limbal or corneal incision).

4. Current evidence of other significant ophthalmic disease requiring topical medication (e.g., glaucoma, ocular hypertension) or other ophthalmic disease which the Investigator believes may interfere with study findings or interpretation.

5. History of corneal transplant in either or both eyes.

6. Diagnosis of recurrent, ongoing, or active ocular infection including, but not limited to herpes simplex or zoster, vaccinia, varicella, tuberculosis of the eye, acanthamoeba, or fungal disease.

7. Use of contact lenses in either eye within 7 days of the Study Visit.

8. Punctal or intracanalicular plug present in either eyelid within 14 days of the Study Visit.

9. Use of regular lid hygiene (all forms of lid care including lid wipes, scrubs and purposeful cleansing of lids with soap or medicated shampoos, etc.) or heat masks within 7 days of the Study Visit.

10. Use of lid heating therapy (i.e., LipiFlow, iLUX, TearCare) or Meibomian gland probing/therapeutic expression within 3 months of the Study Visit.

11. Use of Intense Pulsed Light therapy on eyelids within 3 months of the Study Visit.

12. Use of any topical ocular anti-inflammatory medications (e.g., ocular cyclosporine [Restasis, Cequa, Vevye, generics], lifitegrast [Xiidra]), or any other prescription ophthalmic product for DED (e.g., perfluorohexyloctane [Meibo]), any topical ocular corticosteroid, or any non-steroidal-anti-inflammatory agents within 30 days of the Study Visit.

13. Use of topical ocular autologous serum within 30 days of the Study Visit.

14. Use of any other topical ocular drop (prescription or OTC, including artificial tears) within 2 hours of the Study Visit.

15. Use of Tyrvaya (varenicline solution, nasal spray 0.03mg) within 30 days of the Study Visit.

16. Use of medications for the treatment of severe DED and/or Meibomian gland disease such as oral pilocarpine, oral cevimeline, oral macrolides, oral tetracyclines, oral tetracycline derivatives, and oral retinoids within 30 days of the Study Visit.

General/Systemic:

17. Initiation, discontinuation, or change in dose of a systemic medication known to cause ocular drying (e.g., antihistamines or tricyclic antidepressants) within 7 days of the Study Visit.

18. Initiation, discontinuation, or change in dose of a systemic corticosteroid within 14 days of the Study Visit.
    Note: Non-ocular topically applied corticosteroids (including topical creams, nasal sprays and inhalers) are not applicable to this exclusion.

19. Initiation, discontinuation, or change in dose of a systemic immunomodulator (e.g., hydroxychloroquine, methotrexate, cyclosporine) within 30 days of the Study Visit.

20. Have received any vaccine within 3 days prior to the Study Visit.

21. Use of an investigational product or device within 30 days of the Study Visit.

22. At the Study Visit, at the Investigator's discretion, have uncontrolled or severe:

    a. Systemic allergy

    b. Rhinitis or sinusitis

23. History or presence of significant systemic disease (i.e., cardiovascular, pulmonary, hepatic, renal, hematologic, immunologic). Significant is defined as any disease that, in the assessment of the Investigator, would put the safety of the subject at risk through participation, or would prevent or confound protocol-specified assessments (e.g., severe Sjögren's syndrome, severe rheumatoid arthritis, severe systemic lupus erythematosus, uncontrolled immunodeficiency disease, etc.).

24. Known allergies or sensitivity to the study interventions or study diagnostic agents.

25. Positive pregnancy test or currently breastfeeding.

26. The subject has a condition or is in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.

8.5 Withdrawal Criteria (if applicable)

If at any time during the study the Investigator determines that a subject's safety has been compromised, the subject may be withdrawn from the study.

Subjects may withdraw consent from the study at any time.

The sponsor and/or Investigator may discontinue any subject for non-compliance or any valid medical reason (see Section 11.13.2).

9 STUDY PARAMETERS

9.1 Measures and Endpoints

9.1.1 Primary Measure(s)

- Proportion of ocular AEs reported by intervention arm (512 vs. Refresh Classic).

9.1.3 Safety Measures

- Corrected Visual Acuity
- Slit-Lamp Biomicroscopy
- Adverse Events (AEs)

10 STUDY MATERIALS

10.1 Study Treatment(s)

10.1.1 Study Intervention/Formulation

- AR-15512 ophthalmic solution 0.003%
- Refresh Classic

10.1.2 Instructions for Use and Instillation

This is an acute dosing study, and study interventions are summarized in Table 3. Post enrollment, all subjects will first have 1 drop of Refresh Classic, instilled to the right eye only. Subjects will then receive a total of four drops of 512, instilled sequentially to only 1 eye, starting with the left eye. After the first 2 drops of 512 are instilled, a wait period of 2 to 3 hours must elapse prior to instilling the remaining 2 drops. Each instillation will

differ based on the variations described in Table 1. The order of the four 512 instillation variations will be randomized (Table 2).

Table 3 Study Intervention

Intervention Name	Refresh Classic	AR-15512 ophthalmic solution 0.003%
Intervention Description	Artificial tear (Refresh Classic) to be instilled in clinic by site staff as 1 drop in **right eye only**, prior to instillation of 512.	512 administered twice per eye in clinic by site staff. **Note:** Four 512 instillation variations will be utilized (in randomized sequence, starting with the left eye). Each variation will be instilled in only 1 eye. Following the first two instillation variations, a wait period of between 2 to 3 hours must elapse prior to instillation of the remaining two variations.
Use	Experimental	Experimental
Dose Formulation	Ophthalmic solution	Ophthalmic solution
Route of Instillation	Topical	Topical
Duration	Acute (1 day)	Acute (1 day)

10.2 Other Study Supplies

Details of other study supplies can be found in the Manual of Procedures.

11 STUDY METHODS AND PROCEDURES

11.1 Subject Entry Procedures

11.1.1 Overview

Subjects, as defined by the criteria in Sections 8.2, 8.3, and 8.4, will be considered for entry into this study.

11.1.2 Informed Consent

Written informed consent will be obtained from each subject. 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 study files at the Investigator's site. Signed informed consent must be attained prior to conducting any study procedures.

The Investigator is responsible for ensuring that no subject completes any study-related procedures or activity before that subject has given informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject.

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, but this will not impact their subsequent care.

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 s/he does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian will be required to sign and date the ICF.

11.1.3 Washout Intervals

Prohibited medications and treatments are outlined in Exclusion Criteria (Section 8.4).

11.1.4 Procedures for Final Study Entry

Subjects must meet all inclusion and none of the exclusion criteria.

11.1.5 Methods for Assignment to Treatment Groups

Each subject who signs an ICF will be assigned a screening number. Screening numbers will be assigned in sequential order at each site beginning with 5001 and will follow the four-digit site number (e.g., subject 5001 at Site 9999 will have Screening Number 9999-5001). All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. Inclusion and exclusion criteria will be reviewed, and qualifying subjects will be enrolled in the study.

11.2 Demographics

Demographic data including age, sex at birth, race, and ethnicity will be collected and recorded.

11.3 Medical and Surgical History

Significant medical and ophthalmic history will be collected and any current underlying medical/ophthalmic conditions, including those that may have resolved before the Study Visit, must also be recorded per the Manual of Procedures. All relevant medical and ophthalmic surgical procedures must be recorded.

11.4 Prior and Concomitant Medications

Any medication (including vaccines, OTC, prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of the Study Visit must be recorded on the subject's source document and corresponding electronic case report form (eCRF) along with the reason the medication was taken. Prior medications taken up to at least 30 days prior to the Study Visit must also be recorded.

Concurrent enrollment in another investigational drug or medical device study is not permitted.

11.4.1 Prohibited Medications/Treatments

Disallowed medications/treatments during the study are outlined in the Exclusion Criteria (Section 8.4).

11.4.2 Escape Medications

No escape medications are required for this study.

11.4.3 Special Diet or Activities

No special diets or activities are required for this study.

11.5 Clinical Laboratory Tests

11.5.1 Pregnancy Testing

Urine pregnancy tests for women of childbearing (WOCBP) are required. Pregnancy tests must be negative for the subject to receive study intervention.

An adult woman is considered to be of childbearing potential unless she is at least 1 year post-menopause (no menses for 12 months or more without an alternative medical cause) or at least 3 months post-surgical sterilization.

11.6 Dispensing Study Intervention

Study intervention will be instilled at the Study Visit only by site staff. Details of dosing are displayed in Figure 1 and further details will be provided in the Manual of Procedures.

11.7 Collection of Study Intervention

Used vials should be destroyed per site standard procedures after each instillation.

The number of unused vials will be recorded at site inventory level, and returned to depot at end of study.

11.8 Safety Assessments

11.8.1 Corrected Visual Acuity

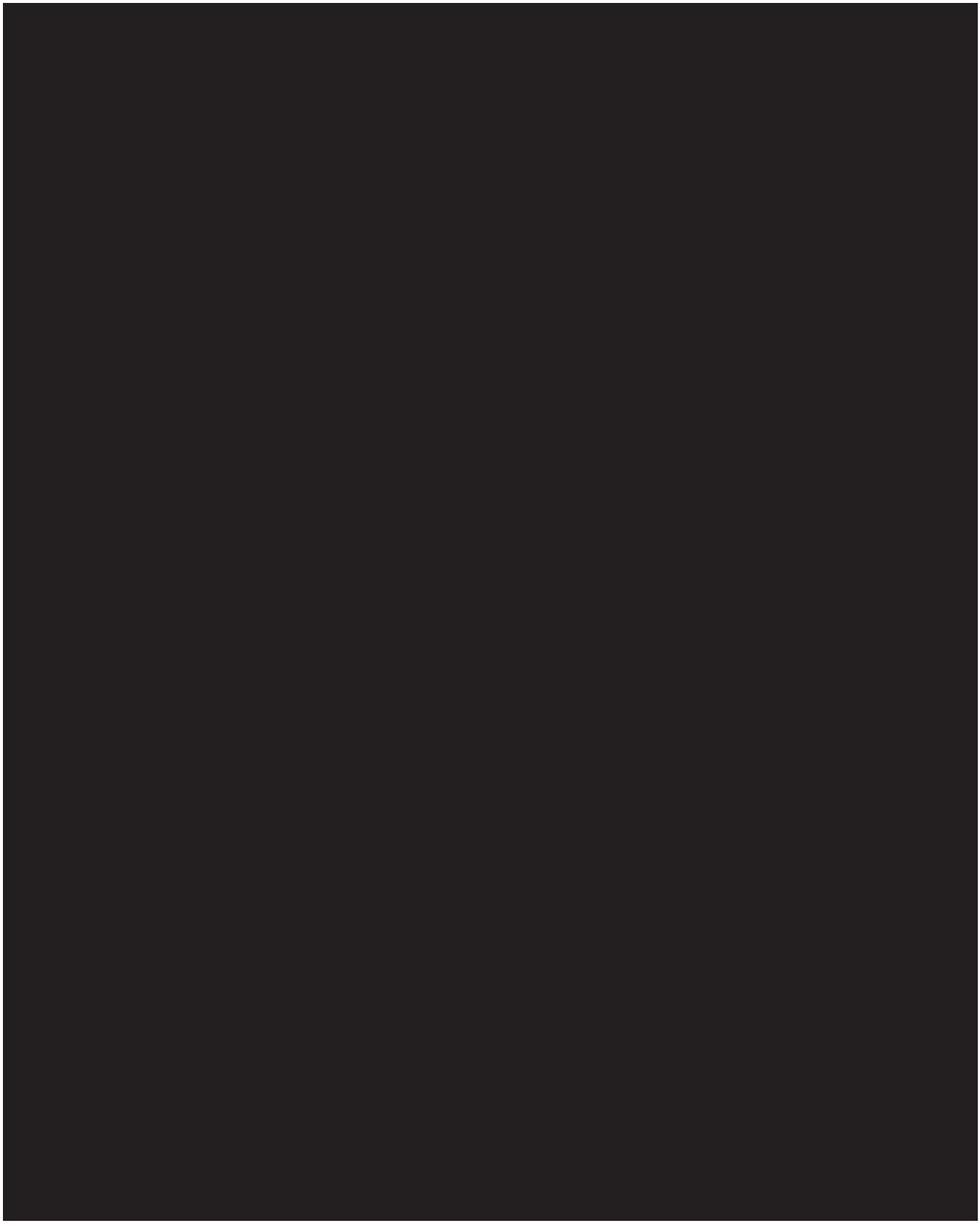
Monocular logarithmic minimum angle of resolution (LogMAR) corrected visual acuity in both eyes must be assessed using an Early Treatment of Diabetic Retinopathy Study (ETDRS) Series 2000 chart. Corrected visual acuity should be evaluated prior to all other ocular examinations as specified in the Schedule of Procedures (Appendix 1). Additional procedural details can be found in the Manual of Procedures.

11.8.2 Slit Lamp Biomicroscopy

Slit lamp biomicroscopic observations will be graded as Normal or Abnormal. Abnormal findings will be categorized as clinically significant (findings that may interfere with study parameters or otherwise confound the data as determined by the Investigator) or not clinically significant. The following will be examined in both eyes:

- Eyelid
- Conjunctiva
- Cornea
- Anterior Chamber
- Iris
- Lens

Additional procedural details can be found in the Manual of Procedures.



11.10 Examination Procedures

11.10.1 Procedures to be Performed at Study Visit with Regard to Study Objective(s)

Details of examination procedures can be found in the Manual of Procedures.

11.11 Schedule of Measurements and Dosing

Refer to Appendix 1 for the Schedule of Procedures.

11.12 Compliance with Protocol

A protocol deviation occurs when there is any non-adherence to a study procedure or schedule that is specified by the protocol. The term “protocol deviation” includes those departures from the protocol previously described by the term “protocol violation”; all departures from the protocol are now described as protocol deviations, regardless of the potential impact on subject safety. A Protocol Deviation Log shall be maintained by the site(s). Protocol deviations will be summarized in the final clinical study report.

11.13 Subject Disposition

11.13.1 Completed Subjects

A completed subject is one who has not been discontinued from the study.

11.13.2 Discontinued Subjects

Subjects may be discontinued prior to their completion of the study due to:

- Withdrawal by subject
- Withdrawal by Investigator
- AEs
- Protocol deviations
- Administrative reasons (e.g., inability to continue)
- Study termination by sponsor

- Other

Note: In addition, any subject may be discontinued for any sound medical reason.

Notification of a subject discontinuation and the reason for discontinuation will be made to Ora and/or the sponsor and will be clearly documented on the eCRF.

11.13.3 Screen Failures

Subjects who do not meet the criteria for participation in this study (screen failures) may be rescreened for eligibility up to one time if there is a reasonable possibility, in the Investigator's opinion, that the subject might meet the eligibility criteria. It is encouraged for the Investigator to discuss potential rescreening with the sponsor. Rescreened subjects should be assigned a new subject number for every screening/rescreening event.

11.14 Study Termination

The study may be stopped at any time by the Investigator, the sponsor, and/or Ora with appropriate notification.

11.15 Study Duration

An individual subject's participation will involve 1 Visit, lasting approximately 7-8 hours.

11.16 Monitoring and Quality Assurance

During the course of the study, an Ora monitor or designee will make routine site visits to review protocol compliance, assess study intervention (i.e., investigational product [IP]) accountability, and ensure the study is being conducted according to the pertinent regulatory requirements. The review of the subjects' medical records will be performed in a manner that adequately maintains subject confidentiality. Further details of the study monitoring will be outlined in a monitoring plan.

Regulatory authorities of domestic and foreign agencies, quality assurance and or its designees may carry out on-site inspections and/or audits which may include source data checks. Therefore, direct access to the original source data will be required for inspections and/or audits. All inspections and audits will be carried out giving consideration to data protection as well as subject confidentiality to the extent that local, state, and federal laws apply.

11.17 Quality Tolerance Limits

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

12 ADVERSE EVENTS

12.1 Performing Adverse Event Assessments

All AEs occurring during the study, regardless of the assumption of causal relationship, must be documented on the respective eCRF.

Qualified study 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. AE information may be volunteered by the subject or solicited by study personnel through non-leading questions.

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

If a disease is known at the time an AE is reported, this diagnosis should be recorded rather than listing of individual symptoms. However, if a cluster of symptoms cannot be identified as a single diagnosis, each individual event should be reported separately. If a diagnosis is subsequently known, it should be reported as follow-up information.

When recording an AE, the following information should be provided on the study AE eCRF:

1. Action Taken with Study Intervention:
    - None
    - Study Intervention Discontinued
    - Study Intervention Interrupted
2. AE Outcome:
    - Fatal
    - Not Recovered/Not Resolved

- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

13 ADVERSE EVENT DEFINITIONS

The following definitions of terms apply to this section:

- **Adverse event (AE):** any untoward medical occurrence associated with the administration of the study intervention in humans, whether or not considered to be related to the study intervention.
- **Adverse reaction (AR):** any AE for which there is a reasonable possibility that the administration of the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the administration of the drug and the AE.

    a) **Life-threatening AE or life-threatening AR:** an AE or AR 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 AR that, had it occurred in a more severe form, might have caused death.

    b) **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, subject hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events 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. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an SAE when the hospitalization or prolonged hospitalization was for an elective surgical procedure or for a preexisting condition (with no increase in severity).

- **Unexpected AE or unexpected AR:** an AE or AR is considered "unexpected" if it is not listed in the Investigator's Brochure (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.

13.1 Reporting Adverse Events

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

If an event occurs after informed consent but prior to subject enrollment and the commencement of study intervention, it should be recorded as an AE. Any change in the health status after commencement of study intervention should be recorded as TEAEs.

Surgery should not be reported as an outcome of an AE if the purpose of the surgery was diagnostic and the outcome was uneventful.

13.1.1 AEs and Prior Medical History

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 pre-existing condition worsens during the study period beyond what would be expected from the natural progression of that condition.

Symptoms and signs that are consistent with the natural history of DED are not considered reportable AEs but such developments are recorded in the medical history per Section 11.3. Worsening symptoms and signs of DED should be recorded as an AE or SAE only if judged by the Investigator to have unexpectedly worsened in severity and/or frequency or changed in nature at any time during the Study Visit. When recording an unanticipated worsening of DED as an AE, it is important to convey why the development was unexpected.

As this study is specifically asking subjects to describe the ocular sensation they may experience upon instillation of study intervention, generally mild sensations are not to be considered as AEs and should not be documented as such. An ocular AE should only be recorded if the subject reports severe painful or unexpected ocular sensations.

If there is a question as to whether a medical development should be reported as an AE, the Investigator is recommended to contact the sponsor for guidance.

13.1.2 Severity

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- **Mild:** Event is noticeable to the subject but is easily tolerated and does not interfere with the subject's daily activities.
- **Moderate:** Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- **Severe:** Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

A change in increased severity for a reported AE during the Study Visit will be recorded. **Note:** A severe AE is not the same as a serious AE (SAE). Seriousness of an AE (NOT severity) serves as a guide for defining regulatory reporting obligations.

13.1.3 Relationship to Investigational Product

A relationship between the AE and the study intervention or study procedure will be determined by the Investigator, as applicable, for each AE using these explanations:

Not Related: 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.

Unlikely Related: Event is most probably caused by other etiologies such as subject's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between administration and the onset of the AE is incompatible with a causal

relationship. Therefore, there is not a reasonable possibility that the AE was caused by the product, device, or procedure.

Possibly Related: Event follows a reasonable, temporal sequence from the time of study intervention instillation or study procedure and/or follows a known response pattern to the product, device or procedure but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy administered to the subject.

Related: Event follows a reasonable, temporal sequence from the time of study intervention instillation or study 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 study intervention administration or procedure, or improves on stopping the study intervention, or reappears on repeat exposure, or there is a positive reaction at the instillation site.

13.1.4 Expectedness

- AEs or ARs are considered "unexpected" if they are not listed in the Reference Safety Information section of the IB for 512 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 512 and are not specifically mentioned as occurring with the study drug.

- For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or ARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

- An Investigator must immediately (i.e., within 24 hours from time of awareness) report any SAE or SAR (see Section 12.2 for definitions) to the sponsor or its clinical research organization (CRO) representative, whether or not considered drug-related, including those listed in the protocol or IB.

13.2 Serious Adverse Events, Serious Adverse Reactions or Suspected Unexpected Serious Adverse Reactions

13.2.1 Serious Adverse Events

An AE is considered serious if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

a) Death;

b) A life-threatening AE;

Note: An AE 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 that, had it occurred in a more severe form, might have caused death.

c) Inpatient hospitalization or prolongation of existing hospitalization;

Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the Investigator or treating physician.

d) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

Note: A SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).

e) A congenital anomaly/birth defect.

Important medical events that may not result in death, are 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.

13.3 Procedure for Reporting Adverse Events

All AEs and their outcomes must be reported to Ora, the study sponsor, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by the IRB/IEC, federal, state, or local regulations and governing health authorities and recorded on the appropriate eCRF.

13.3.1 Reporting SAEs or SARs

An Investigator must immediately (i.e., within 24 hours) report any SAE or SAR (see Section 12.2 for definitions) to the sponsor or its CRO representative, whether or not considered study intervention-related, including those listed in the protocol or IB. The Investigator must use the SAE report form and include an assessment of whether there is a reasonable possibility that the drug caused the event. The Investigator must report any SAE or SAR that occurs or is observed during the study. In case of incomplete information, the Investigator must provide follow-up information as soon as possible, again using the SAE report form.

SAE reports will be evaluated by the Medical Monitor. Regulatory authorities, IRB, and Investigators at each of the study sites will be informed as required.

13.3.2 Reporting Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Investigator must immediately (i.e., within 24 hours) report SUSARs. In the event of SUSAR, the site must notify the Medical Monitor for the study, submit an SAE report form and record the event within the Electronic Data Capture (EDC) system within 24 hours of notification, or occurrence of the SUSAR, whether or not complete information is available. In the case of incomplete information, the Investigator must provide follow-up information as soon as possible using the SAE report form.

13.3.3 SAE Report Contact Information

[redacted]

[redacted]

13.4 Procedures for Unmasking

This is a subject-masked study; masking procedures to be employed will be described in the Pharmacy Manual as well as the Manual of Procedures.

13.5 Type and Duration of the Follow-up of Subjects after Adverse Events

The Investigator will follow AE outcomes until study completion or the AE is otherwise classified. The outcome of the AE at the time of study completion should be recorded in the AE eCRF. All follow-up will be documented in the subject's source document. Non-serious AEs identified on the last scheduled contact must be recorded on the AE eCRF with the status noted.

If the Investigator becomes aware of any new information regarding an existing SAE (i.e., resolution, change in condition, or new treatment), a new SAE/Unanticipated report form must be completed and faxed to Ora within 24 hours of the site's awareness of the new information. The original SAE form is not to be altered. The report should describe whether the event has been resolved or continues and how the event was treated.

13.6 Drug Technical Events and Device Deficiencies for Drug/Device Combination Products

Any technical events concerning the test article formulations or device deficiencies concerning the ophthalmic delivery device (i.e., blow-fill-seal) must be reported to the sponsor. The Pharmacy Manual provides instructions on how to report to the sponsor.

A drug technical event is a deficiency of any non-device constituents of the study intervention. Non-device constituents include the drug and drug excipients, packaging, information supplied by the manufacturer, and labelling related to the study intervention. Events may include inadequacies in quality, identity, safety, strength, purity, performance, and/or physical characteristics.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Do not use any study intervention suspected to have a drug technical event and/or device deficiency. Isolate the study intervention from other products in the same storage condition until follow-up communication and instructions are received from the sponsor.

A drug technical event or device deficiency may or may not be associated with subject harm. AEs, whether related or not related to technical events or device deficiencies, must be recorded in the AE eCRF.

14 STATISTICAL HYPOTHESES AND METHODS OF ANALYSES

In case of any discrepancies or differences between the protocol and the Statistical Analysis Plan (SAP) concerning descriptions or explanations, including but not limited to the definitions of endpoints or the statistical approach/model for primary, secondary, or exploratory objectives, the SAP shall take precedence and supersede the protocol.

14.1 Analysis Set

The following analysis sets will be considered:

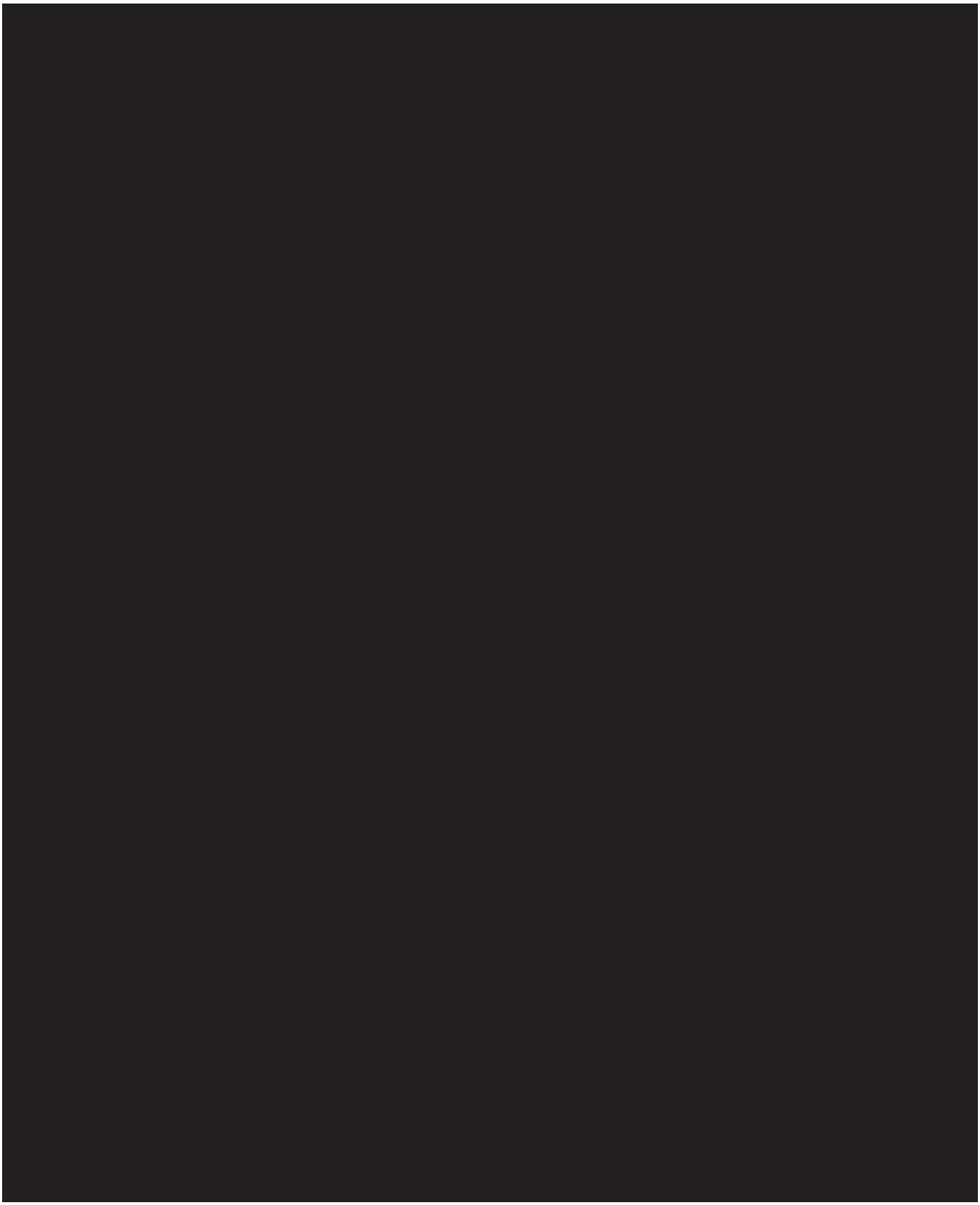
- Safety Analysis Set (SAF): The SAF will include all subjects who received at least one dose of Refresh Classic or one dose of 512.
- Full Analysis Set (FAS): The FAS will include all subjects who have received at least one dose of Refresh Classic and one dose of 512 instillation variation and who have at least one rating of the Rating Sensation Assessment.

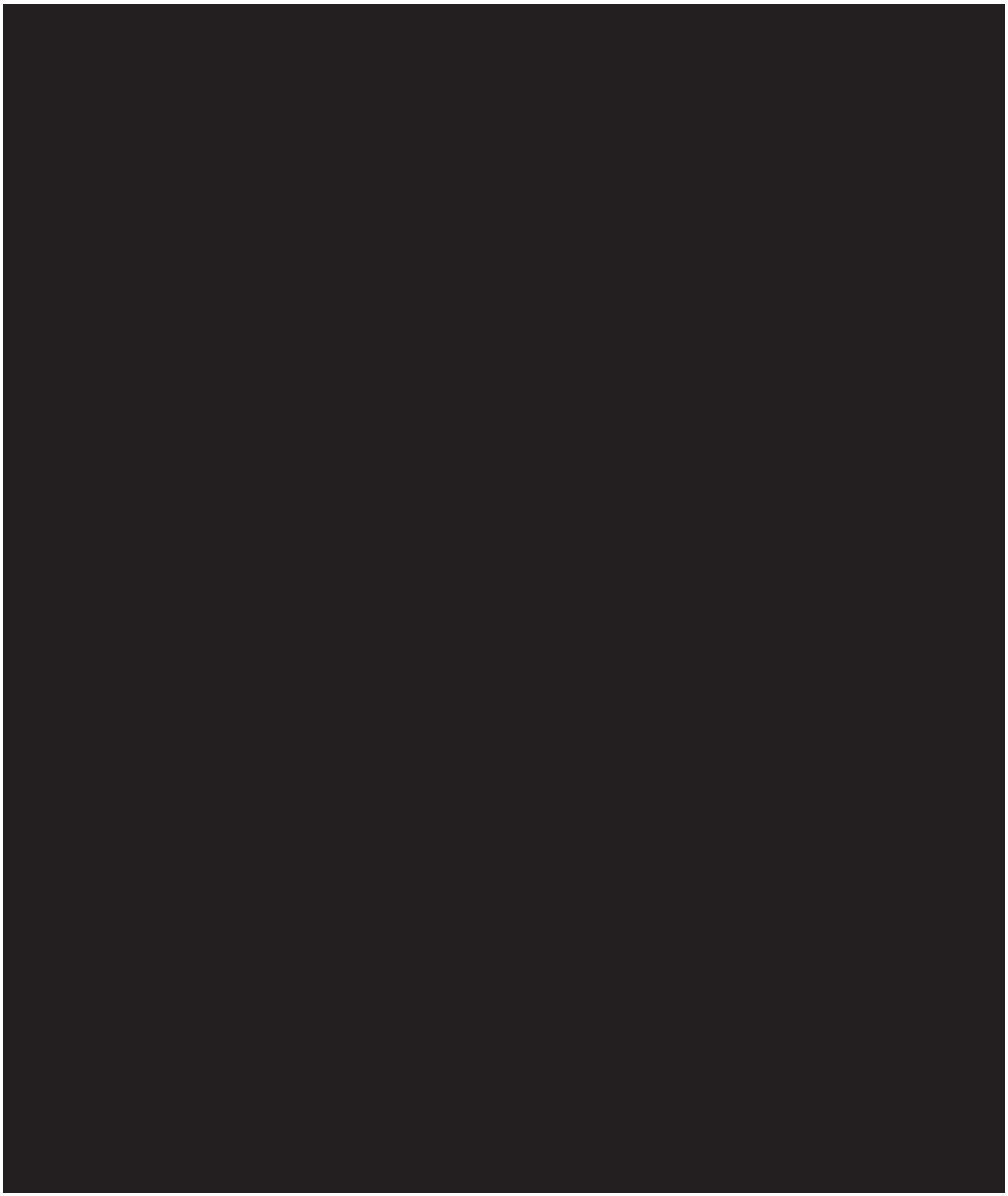
[redacted]

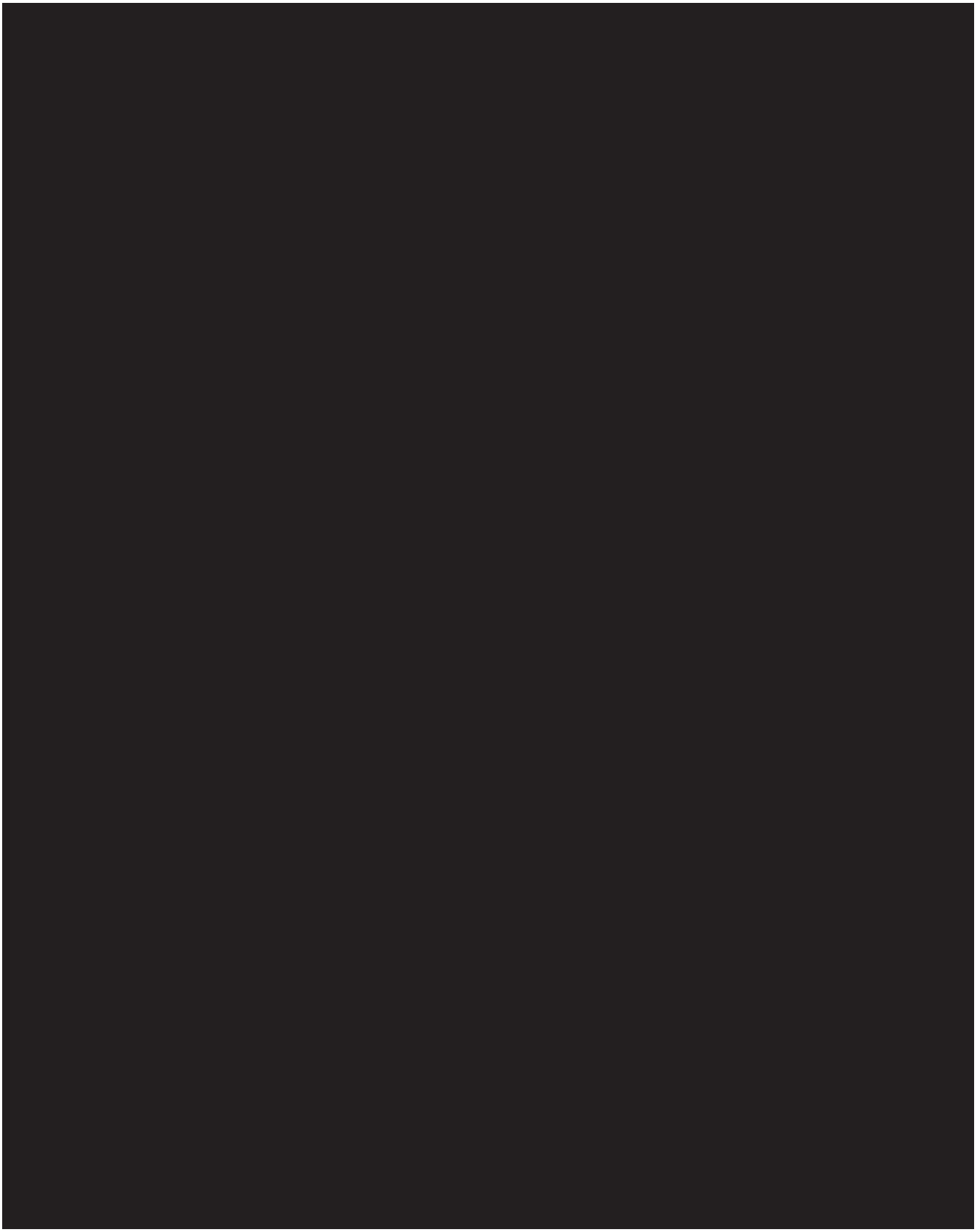
14.2 Analyses Supporting Primary and Secondary Objectives(s)

This Phase 3b does not have any efficacy objectives. For the safety primary objective, descriptive summaries, including counts and frequencies will be reported by intervention arm. Additional details will be presented in the SAP.

[redacted]







14.4 Statistical Model, Hypotheses and Methods of Analysis

No formal pre-planned Type I error rate will be controlled, meaning no specific threshold for false positives will be set beforehand. While p-values will be reported, results should be interpreted with caution.

14.5 Safety Analysis

AEs will be collected after the subject signs the ICF and coded using the latest MedDRA version. TEAEs will be summarized using the SAF by system organ class and preferred term. Other safety parameters collected will be summarized.

14.6 Sample Size Determination

No power calculation will be used to determine the sample size. [redacted] The study aims to recruit approximately 36 to 55 subjects.

14.7 Interim Analyses

No interim analysis will be performed in this study.

15 COMPLIANCE WITH GOOD CLINICAL PRACTICES, ETHICAL CONSIDERATIONS, AND ADMINISTRATIVE ISSUES

This study will be conducted in compliance with the protocol, current Good Clinical Practices (GCPs), including the International Conference on Harmonization (ICH) Guidelines, and in general, consistent with the Declaration of Helsinki. In addition, all applicable local, state, and federal requirements relevant to the use of IP in the countries involved will be adhered to.

15.1 Protection of Human Subjects

15.1.1 Subject Informed Consent

Informed consent must take place before any study-specific procedures are initiated. Signed and dated written informed consent must be obtained from each subject and/or from the subject's parent or legal guardian prior to enrollment into the study.

All informed consent forms must be approved for use by the sponsor and receive approval/favorable opinion from an IRB/IEC prior to their use. If the ICF requires revision (e.g., due to a protocol amendment or significant new safety information), it is the Investigator's responsibility to ensure that the amended informed consent is reviewed and approved by Ora prior to submission to the governing IRB/IEC and that it is read, signed, and dated by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

If informed consent is taken under special circumstances (oral informed consent), then the procedures to be followed must be determined by Ora and/or sponsor and provided in writing by Ora and/or sponsor prior to the consent process.

15.1.2 Institutional Review Board Approval

This study is to be conducted in accordance with IRB regulations (U.S. 21 Code of Federal Regulations [CFR] Part 56.103). The Investigator must obtain appropriate IRB approval before initiating the study and re-approval at least annually.

Only an IRB/IEC-approved version of the informed consent form will be used.

15.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that originated with the Declaration of Helsinki.

15.3 Subject Confidentiality

All personal study subject data collected and processed for the purposes of this study should be maintained by the Investigator and his/her staff with adequate precautions as to ensure that the confidentiality of the data is in accordance with local, state, and federal laws and regulations.

Monitors, auditors, and other authorized representatives of Ora, the sponsor, the IRB/IEC approving this study, the Food and Drug Administration, the Department of Health and Human Services, other domestic government agencies, and other foreign regulatory agencies will be granted direct access to the subject's original medical and study records for verification of the data and/or clinical trial procedures. Access to this information will be permitted to the aforementioned individuals to the extent permitted by law.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the IP may ultimately be marketed, but the subject's identity will not be disclosed in these documents.

15.4 Documentation

Source documents may include a subject's medical records, hospital charts, clinic charts, the Investigator's study subject files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and EKGs. The Investigator's copy of the CRFs serves as the Investigator's record of a subject's study-related data.

15.4.1 Retention of Documentation

All study-related correspondence, subject records, consent forms, records of the distribution and use of all IP, and copies of CRFs should be maintained on file for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or until at least two years have elapsed since the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian.

15.5 Labeling, Packaging, Storage, Accountability, and Return or Disposal of Investigational Product

15.5.1 Labeling/Packaging

The IP will be packaged into pouches. All pouches will be labeled according to applicable regulatory requirements.

Refresh Classic will remain in the commercial packaging. A label with the protocol number will be applied to the outer carton.

15.5.2 Storage of Investigational Product

The IP must be stored in a secure area accessible only to the Investigator and his/her designees. The IP will be administered only to subjects entered into the clinical study, in accordance with the conditions specified in this protocol. The IP should be stored at refrigerated conditions (2 to 8°C / 36 to 46°F) upon receipt. See more details in the Pharmacy Manual.

Note: Refresh Classic will be stored in accordance with the manufacturer's instructions.

15.5.3 Accountability of Investigational Product

The IP is to only be prescribed by the Principal Investigator or his/her named sub-Investigator(s) and is to only be used in accordance with this protocol. The IP must only be administered to subjects properly qualified under this protocol to receive IP.

The Investigator must keep an accurate accounting of the IP received from the supplier. This includes the amount of IP dispensed to subjects, and the amount returned to the supplier upon the completion of the study. A detailed inventory must be completed for the IP.

15.5.4 Return or Disposal of Investigational Product

When the study is completed or is terminated by the sponsor, all study materials including unused IP pouches/vials will be returned to the sponsor or their designee. All IP accounting procedures must be completed before the study is considered to be concluded. The responsible person(s) at the Investigator’s site has the sole responsibility to account for all used, partially used, and unused IPs. This site staff member at the Investigator’s site will complete a study intervention returns form or equivalent that will be signed by the Investigator or designee prior to returning the unused IP pouches/vials to the sponsor or their designee.

15.6 Recording of Data on Source Documents and Case Reports Forms

The Investigator is responsible for ensuring that study data is completely and accurately recorded on each subject’s CRF, source document, and all study-related material. All study data should also be attributable, legible, contemporaneous, and original. Recorded data should only be corrected in a manner that does not obliterate, destroy, or render illegible the previous entry (e.g., by drawing a single line through the incorrect entry and writing the revision next to the corrected data). An individual who has corrected a data

entry should make clear who made the correction and when by adding to the correction his/her initials as well as the date of the correction.

15.7 Handling of Biological Specimens

Not applicable.

15.8 Publications

Authorship and manuscript composition will reflect cooperation among all parties involved in the study. Authorship will be established before writing the manuscript. Ora and the sponsor will have the final decision regarding the manuscript and publication.

16 REFERENCES

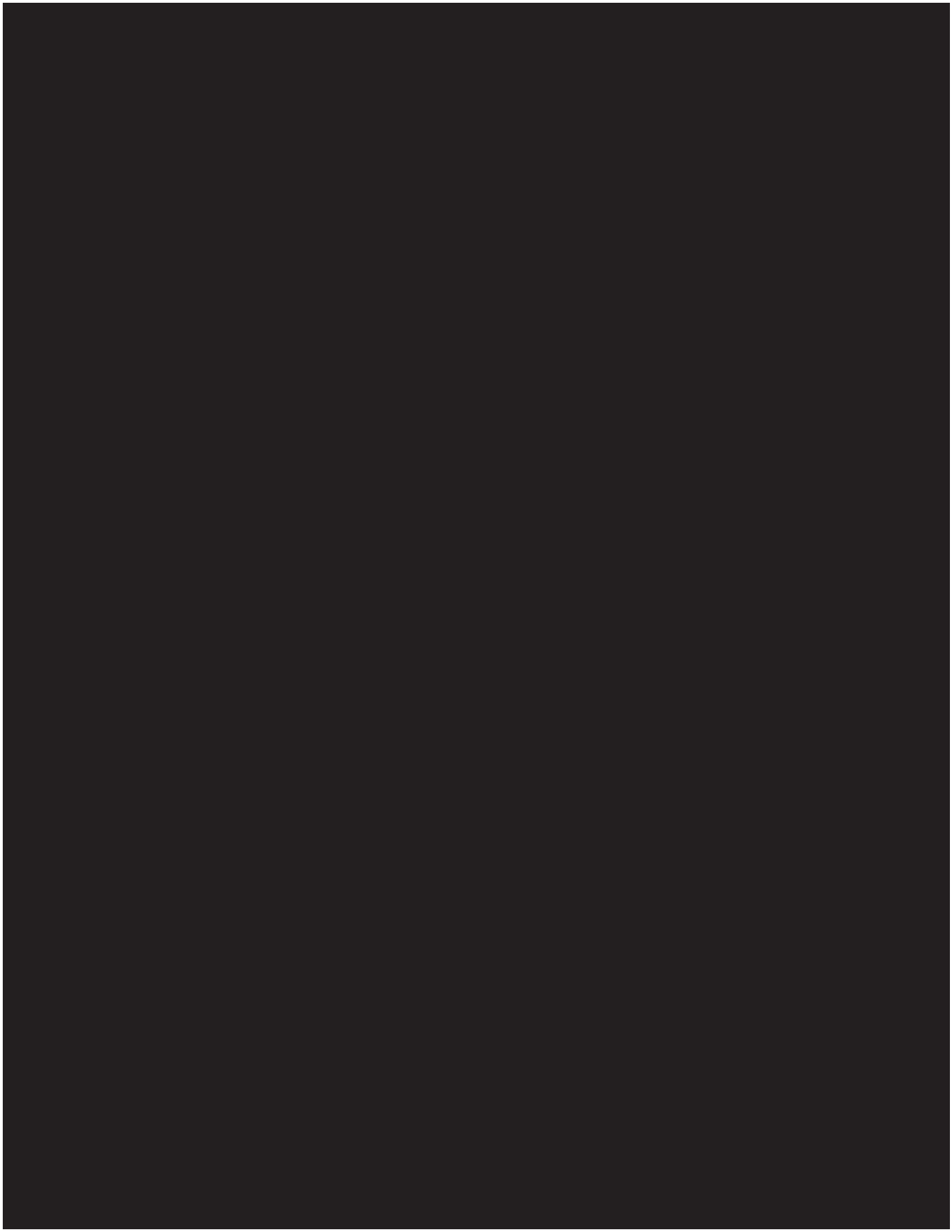
Craig, J. P., K. K. Nichols, E. K. Akpek, B. Caffery, H. S. Dua, C. K. Joo, Z. Liu, J. D. Nelson, J. J. Nichols, K. Tsubota and F. Stapleton (2017). "TFOS DEWS II Definition and Classification Report." Ocul Surf **15**(3): 276-283.

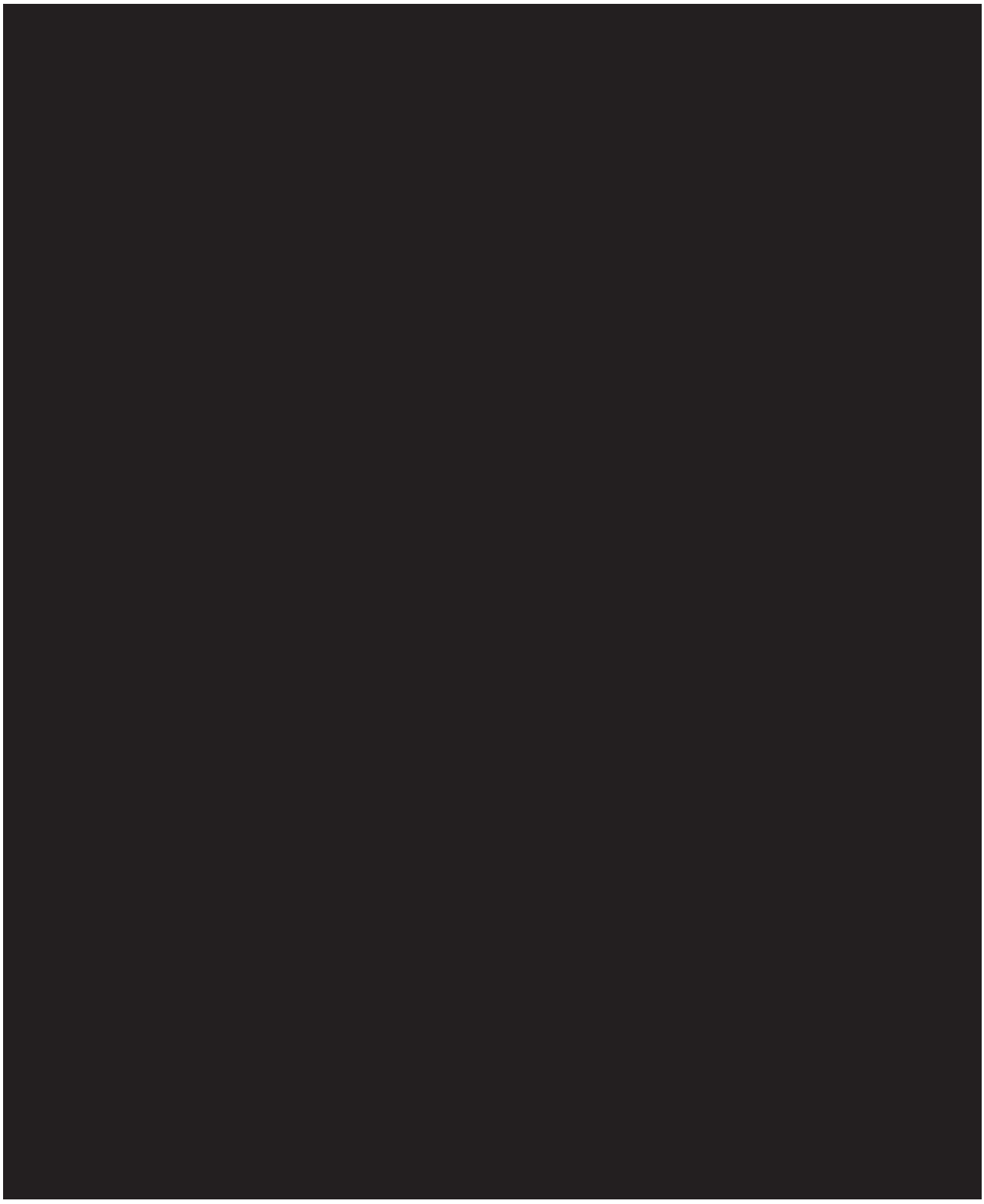
17 APPENDICES

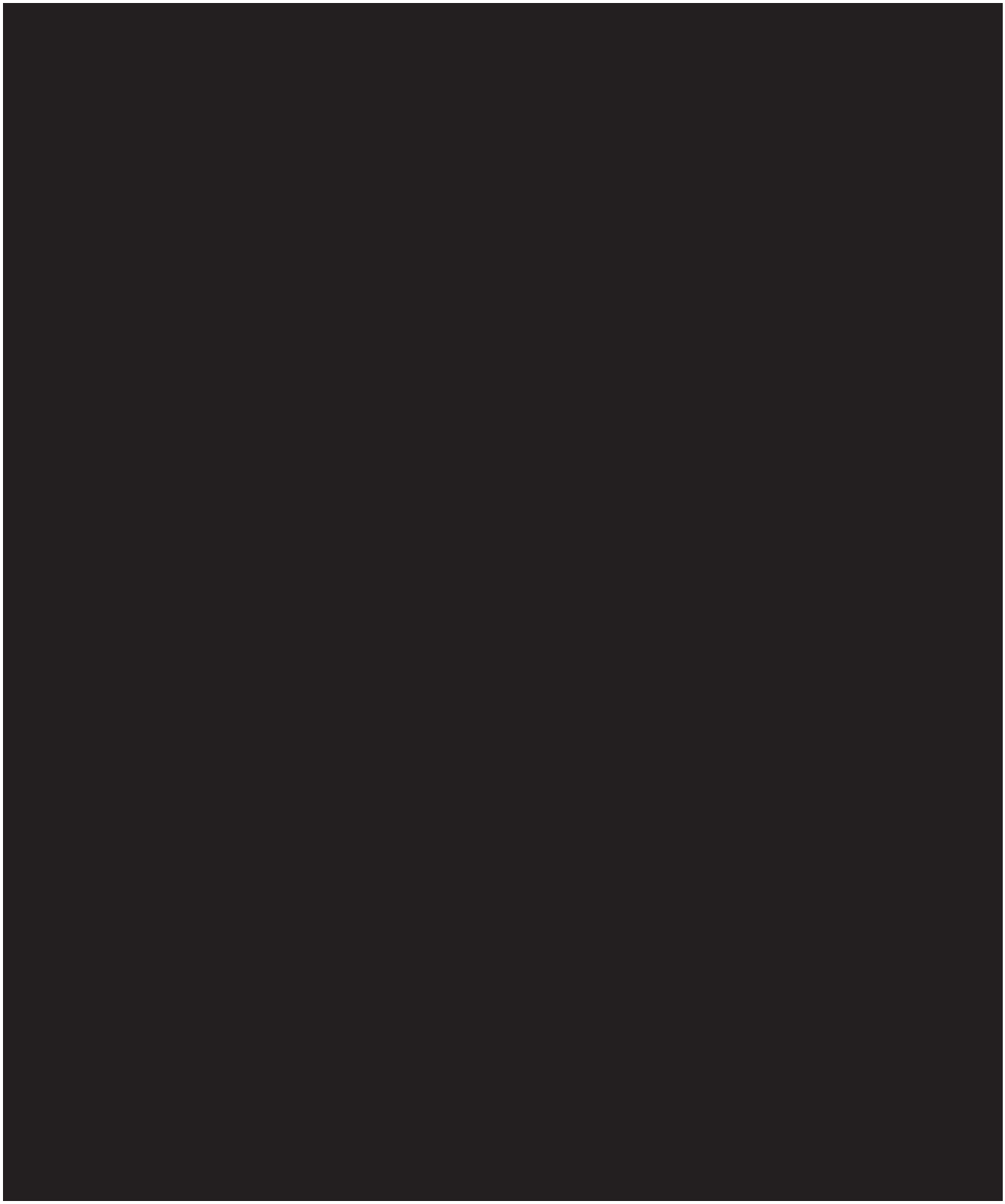
APPENDIX 1: SCHEDULE OF PROCEDURES

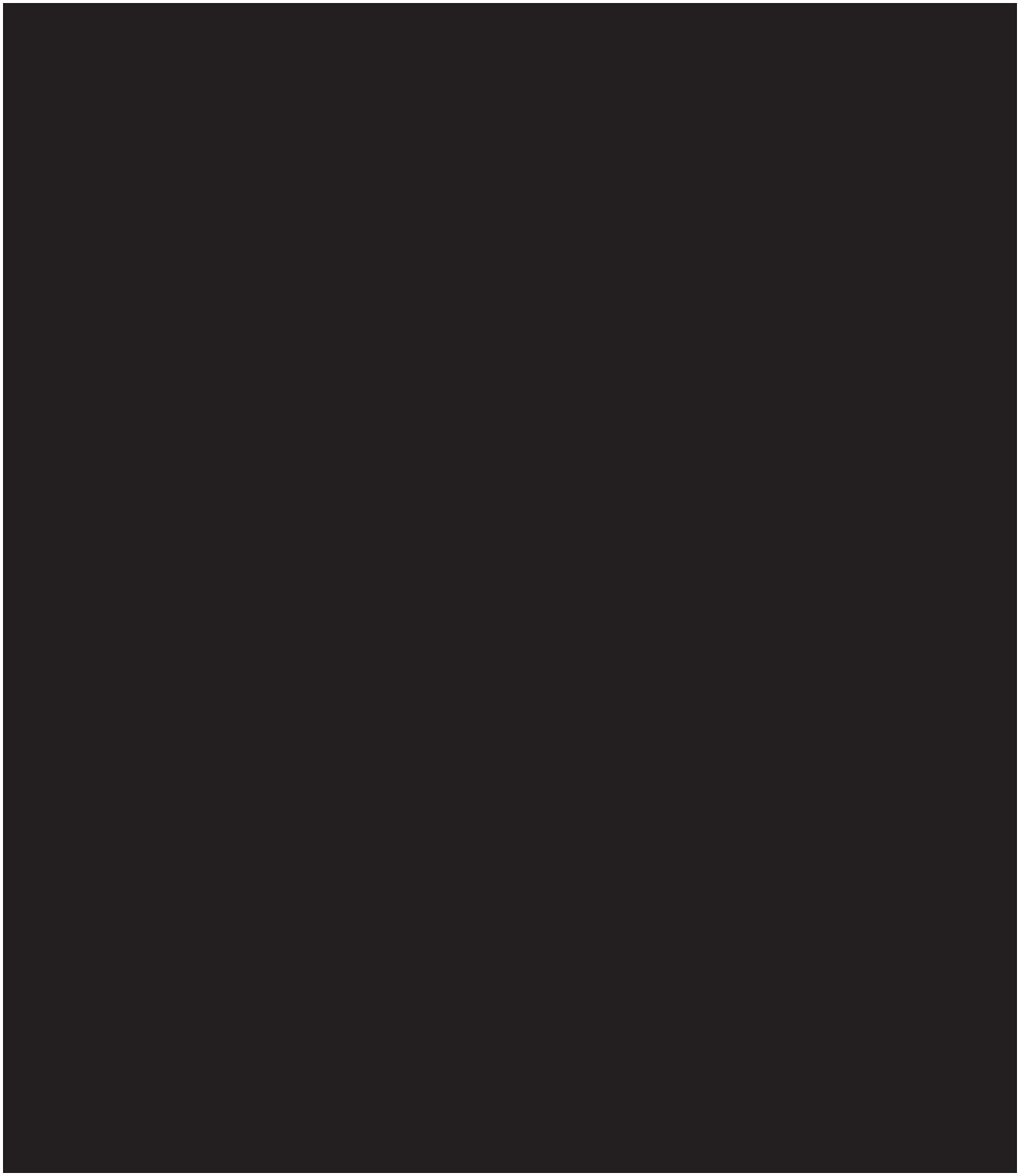
Assessment	
Informed consent	X
Demographics	X
Medical, ophthalmic, and surgical history	X
Prior or concomitant medication review	X
Urine pregnancy test (WOCBP only)	X
Corrected visual acuity *(pre-drop)*	X
Slit lamp biomicroscopy *(pre-drop)*	X
Inclusion and exclusion criteria review	X
Study Enrollment	X
Instillation of 1 drop of Refresh Classic to right eye	X
[redacted]	
30 min ± 5 min wait	X
Randomization to order the sequence of 512 instillation variation (may occur during the 30 min ± 5 min wait period)	X
Instill **first** randomized 512 instillation variation to left eye	X
[redacted]	
30 min ± 5 min wait	X
Instill **second** randomized 512 instillation variation to right eye	X
[redacted]	
Minimum 2 hour and Maximum 3 hour wait	X
Instill **third** randomized 512 instillation variation to left eye	X
[redacted]	
30 min ± 5 min wait	X
Instill **fourth** randomized 512 instillation variation to right eye	X
[redacted]	

Assessment	
[redacted]	
Corrected visual acuity *(post-last drop)*	X
Slit lamp biomicroscopy *(post-last drop)*	X
Adverse events	X
Study Exit	X
Abbreviations: min = minutes; WOCBP = women of childbearing potential	









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Parties agreed to: Abby Jimoh, Agustin Calatroni, Cecilia Chao, George Ousler, Michelle Senchyna