STATISTICAL ANALYSIS PLAN

A Multi-Center, Phase 2, Randomized, Double-Masked, Parallel-Group, Vehicle-Controlled, Clinical Trial to Assess the Safety and Efficacy of Reproxalap Ophthalmic Solution (0.25% Novel Formulation) Compared to Vehicle in Subjects with Dry Eye Disease

Sponsor: Aldeyra Therapeutics, Inc.

Protocol Number: ADX-102-DED-013

Author: [redacted]

Date: 30-DEC-2019

Version: 2.0

SMC
Statistics & Data Corporation

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Statistical Analysis Plan Approval

[redacted]

Prepared by:

Reviewed by:

Approved by:

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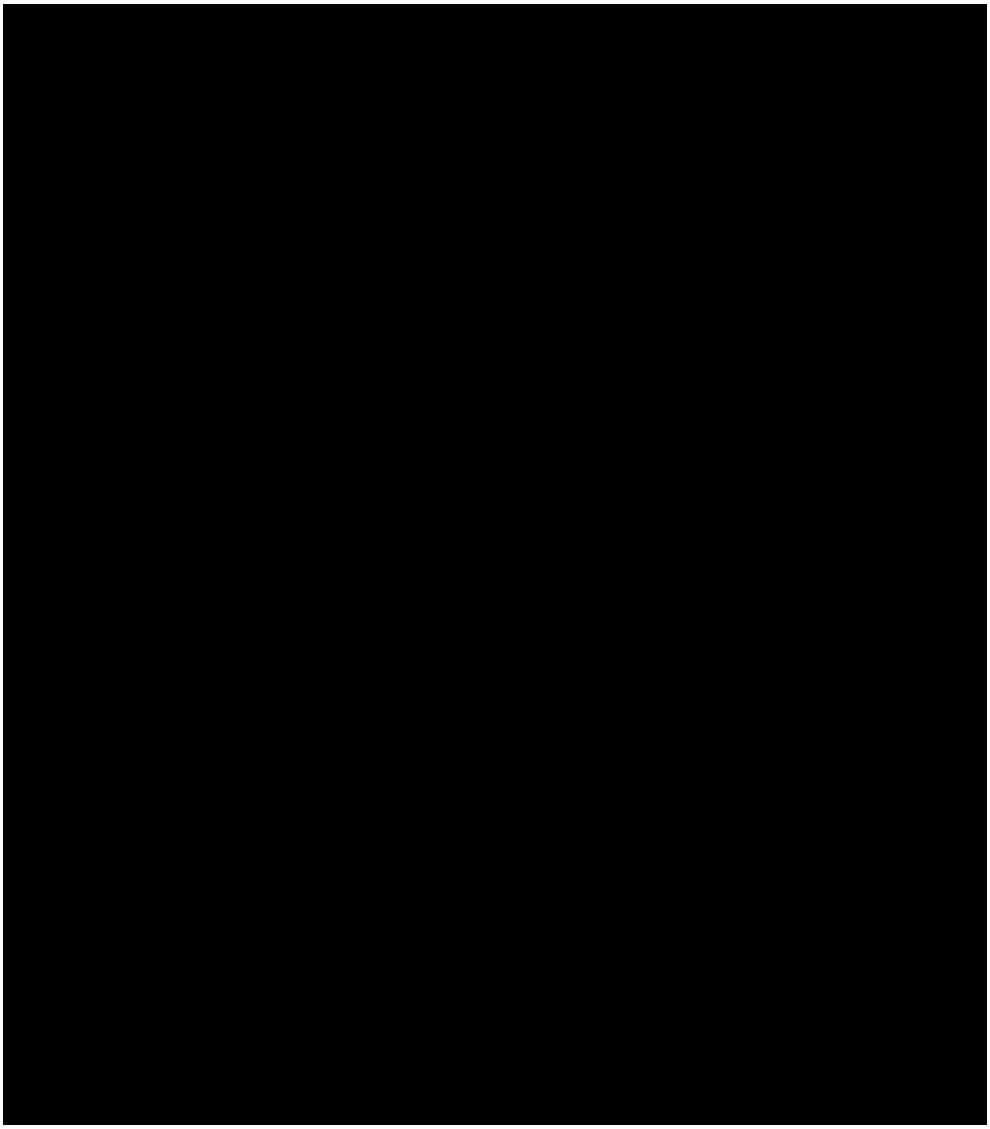

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CAC	Conjunctival Allergen Challenge
CAE	Controlled Adverse Environment
CI	Confidence Interval
CRO	Contract Research Organization
CS	Clinically Significant
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FSN	Fluorescein Staining of the Nasal Region
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
ITTFSN	Intent-to-Treat Fluorescein Nasal Score
ITTOD	Intent-to-Treat Ocular Dryness
IWRS	Interactive Web Response System
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of Mercury
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
mOsm	Milliosmoles
NCS	Not Clinically Significant
OD	*Oculus Dexter* (Right Eye)
OS	*Oculus Sinister* (Left Eye)
OSDI	Ocular Surface Disease Index

OU	*Oculus Uterque* (Both Eyes)
PDF	Portable Document Format
PP	Per Protocol
PPOD	Per Protocol Ocular Dryness
PPFSN	Per Protocol Fluorescein Nasal Score
PT	Preferred Term
QID	*Quater in Die* (Four Times Daily)
RTF	Rich Text Format
SAE	Serious Adverse Event
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SDC	Statistics & Data Corporation, Incorporated
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TMF	Trial Master File
VA	Visual Acuity
VAS	Visual Analog Scale
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ADX-102-DED-013, amendment 1 dated 17 December 2019.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

2.1 Primary Measures

The primary efficacy measure for the trial are the following:

- [redacted] ocular dryness score measured by the Visual Analog Scale [redacted]

[redacted]

[redacted]

[redacted]

2.5 Safety Measures

The safety measures for the trial include the following:

- [redacted]

- [redacted]

2.6 Statistical Hypotheses

The following hypothesis will be tested [redacted]

3. Study Design and Procedures

3.1 General Study Design

The clinical trial is a Phase 2, multicenter, randomized, double–masked, parallel-group, vehicle-controlled design with block enrollment. Subjects will be randomized to one of the following treatment groups at Visit 2 and will be instructed to follow a dosing regimen QID dosing for four weeks followed by BID dosing for weeks 5-12:

- Reproxalap Ophthalmic Solution (0.25% Novel Formulation)
- Vehicle Ophthalmic Solution (vehicle)

Approximately 200 subjects will be randomly assigned to one of the two treatment groups (1:1) to receive either Reproxalap Ophthalmic Solution (0.25% Novel Formulation) or vehicle solution as topical ophthalmic drops administered bilaterally QID for four weeks followed by BID dosing for weeks 5-12. Subjects, Sponsor, CRO and site personnel will be masked to treatment assignment.

During the screening period, two [redacted] exposures to the CAE® will be conducted to ascertain eligibility to enter the study. Those who qualify will be randomized to receive study drug in a double-masked fashion for 84 days. Subjects will self-administer drops daily as instructed.

[redacted]

All subjects will dose with randomized treatment QID [redacted]

The total number of expected participants, including screen failures, is approximately [redacted].

Subjects who terminate early during the treatment period will be asked to complete safety assessments prior to commencement of alternative DED therapy (if possible). Subjects who are terminated early from the study will not be replaced.

Subjects, the Sponsor, the CRO, investigators, and site personnel will be masked to treatment assignment.

Table 1 shows the scheduled study visits, their planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

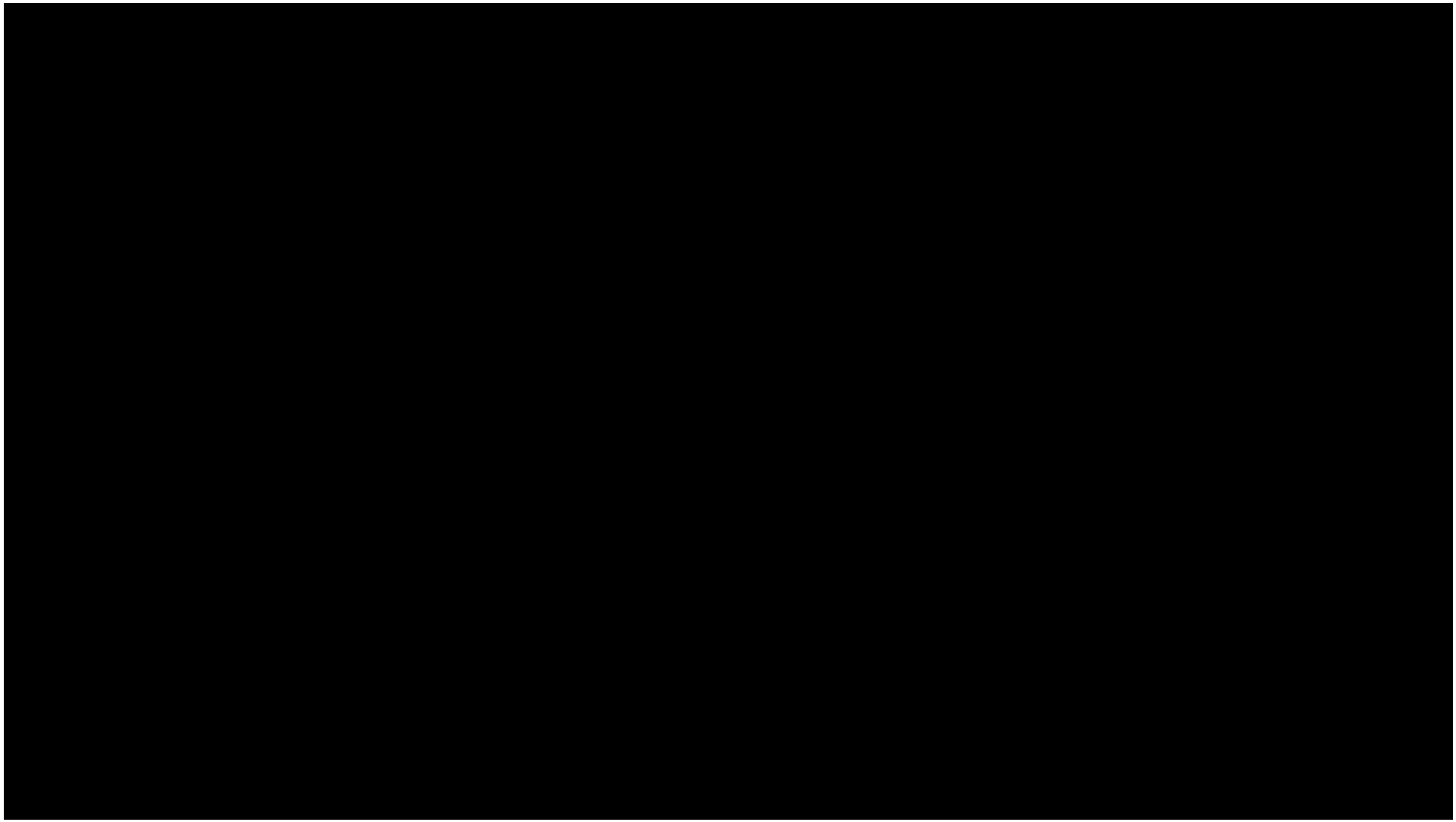
Table 1. Scheduled Study Visits, Planned Study Days, and Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -14	± 2 Days
Visit 2	Day 1	N/A
Visit 3	Day 8	± 2 Days
Visit 4	Day 15	± 2 Days
Visit 5	Day 29	± 2 Days
Visit 6	Day 43	± 2 Days
Visit 7	Day 57	± 3 Days
Visit 8	Day 71	± 3 Days
Visit 9	Day 85	± 3 Days

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below for the study.

Table 2. Schedule of Visits and Measurements



4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Arms

Before the initiation of study run-in at Visit 1 (Day -14), each subject who provides written and informed consent will be assigned to a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will be skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 (Day -14) and Visit 2 (Day 1) will be assigned a randomization number at the end of Visit 2 (Day 1). The Interactive Web Response System (IWRS) will be used to assign all randomization numbers.

[redacted]

Randomization and kit numbers will be assigned automatically to each subject as they are entered into the IWRS.

The site staff will dispense kit(s) required until the next visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). The Sponsor, investigators, and study staff will be masked during the randomization process and throughout the study.

4.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to study drug treatment assignments. When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the Sponsor should be notified before unmasking IP. Ora and/or the study Sponsor must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, he/she should contact Ora and/or the medical monitor prior to unmasking the identity of the IP, if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify Aldeyra and jointly will determine if the unmasking request should be granted. They may consult the medical monitor

as needed. The result of the request will be documented on the Unmasking Request Form. If approval is granted to unmask a subject, written permission via the Unmasking Request Form will be provided to the investigator. The investigator will unmask the subject using IWRS. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the TMF (Trial Master File). For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject, must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study.

5. Sample Size and Power Considerations

Based on the results of a Phase 2b clinical trial [redacted]

6. Data Preparation

Electronic Case Report Forms (eCRF) will be developed by Statistics & Data Corporation, Incorporated (SDC). Unless otherwise specified by Aldeyra, the eCRFs will follow SDTM standards. Data from source documents will be entered into the eCRF by site personnel.

The clinical study database will be developed and tested in [redacted]

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of Aldeyra and Ora in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- [redacted]

- [redacted]

7. Analysis Populations

7.1 Intent-to-Treat

Intent-to-Treat Population: [redacted]

- [redacted]
- [redacted]

7.2 Per Protocol

Per-Protocol Population: [redacted]

- [redacted]
- [redacted]

7.3 Safety

Safety Population: [redacted]

8. General Statistical Considerations

8.1 Unit of Analysis

Safety endpoints will be analyzed [redacted]

[redacted]

8.2 Missing or Inconclusive Data Handling

The primary analyses using MMRM method will be performed [redacted]

8.3 Definition of Baseline

Baseline measures are [redacted]

8.4 Data Analysis Conventions

All data analysis will be performed by SDC [redacted]

[redacted]

[redacted]

8.5 Adjustments for Multiplicity

[redacted]

9. Disposition of Subjects

Subject disposition will be presented [redacted]

[redacted]

[redacted]

[redacted]

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected [redacted]

10.2 Pretreatment Variables

Baseline disease characteristics will be summarized [redacted]

11. Medical History and Concomitant Medications

11.1 Medical History

Ocular medical history will be summarized [redacted]

[redacted]

Listings of medical history will be generated separately for ocular and non-ocular data.

11.2 Concomitant Medications

Ocular and non-ocular concomitant medications will be coded [redacted]

Listings of concomitant medications will be generated separately for ocular and non-ocular data.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Dosing compliance [redacted]

- [redacted]

[redacted]

A subject listing of dosing compliance and study drug accountability will also be produced.

A subject listing of run-in, run-in instillation, and run-in replacement will be provided as well as study drug assignment, instillation, and replacement.

12.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated [redacted]

[redacted]

Subject listings of study drug exposure and dosing compliance will be produced.

13. Efficacy Analyses

13.1 Primary Analysis

The primary endpoint is [redacted]

[redacted] The primary endpoint will be described in subject listings.

13.1.1 Ocular Dryness Score

The subject will be asked to subjectively rate their ocular dryness [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.2 Key Secondary Analysis

The key secondary endpoint is the overall mean change from baseline in fluorescein nasal region score [redacted] The key secondary endpoint will be described in subject listings.

13.2.1 FLUORESCEIN NASAL STAINING FROM WEEK 1 TO WEEK 6

Fluorescein nasal staining will be graded using the Ora Calibra® Corneal and Conjunctival Staining Scale [redacted]

13.3 Secondary Analyses

Secondary efficacy variables will be summarized [redacted]

- [redacted]

13.3.1 Fluorescein Nasal Staining from Week 2 to Week 12

Fluorescein nasal staining will be graded using the Ora Calibra® Corneal and Conjunctival Staining Scale [redacted]

13.3.2 Dryness from the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire

Subjects will rate the severity of each of their symptoms [redacted]

[redacted]

13.3.3 FLUORESCEIN STAINING (ORA CALIBRA® SCALE)

Fluorescein staining will be conducted [redacted]

[redacted]

[redacted]

13.3.4 Ocular Dryness (VAS) through Visit 5 (Day 29)

Ocular dryness (OU) will recorded [redacted]

13.3.5 Ocular Dryness Score [redacted]

Ocular dryness score [redacted] will be summarized [redacted]

[redacted]

13.3.6 Fluorescein Nasal Staining [redacted]

Visit-based data will be summarized [redacted]

[redacted]

[redacted]

13.3.7 Fluorescein Nasal Staining [redacted]

Visit-based data will be summarized [redacted]

[redacted]

[redacted]

[redacted]

13.3.8 Dryness from the ORA Calibra® Ocular Discomfort & 4-Symptom Questionnaire [redacted]

Visit-based data will be summarized [redacted]

[redacted]

14. Exploratory Analyses

Exploratory efficacy variables will be summarized [redacted]

- [redacted]

14.1.1 VISUAL ANALOG SCALE

Ocular symptoms of the VAS will recorded [redacted]

[redacted]

14.1.2 Ocular Discomfort Scale (ORA Calibra Scale)

Ocular discomfort scores will be subjectively graded [redacted]

[redacted]

14.1.3 Ocular Discomfort & 4-Symptom Questionnaire (ORA Calibra® Scale)

Subjects will rate the severity of each of the following symptoms [redacted]

[redacted]

[redacted]

14.1.4 Ocular Surface Disease Index©

The OSDI© is assessed [redacted]

[redacted]

14.1.5 Symptom Assessment in Dry Eye

Subjects will be asked to complete the SANDE Questionnaire [redacted]

14.1.6 Conjunctival Allergen Challenge Ocular Itching Scale (ORA Calibra® Scale)

Subjects will rate the severity of their ocular itching symptom [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

14.1.7 LISSAMINE GREEN STAINING (ORA CALIBRA® SCALE)

Subjects will undergo lissamine green staining [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.1.8 TEAR FILM BREAK-UP TIME

The TFBUT will be recorded [redacted]

[redacted]

14.1.9 TEAR OSMOLARITY

Tear osmolarity will be measured [redacted]

14.1.10 UNANESTHETIZED SCHIRMER'S TEST

Unanesthetized Schirmer's test will be conducted [redacted]

[redacted]

15. Safety Analyses

All safety analyses will be conducted using the Safety population.

15.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose.

All AEs will be coded using the MedDRA 22.0.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated. Adverse events recorded in the eCRF which began prior to treatment will not be included in the summary tables but will be included in the AE data listings.

An overall summary will be presented that includes the number and percentage of subjects who experienced at least one AEs, ocular AEs, non-ocular AEs, SAEs, AEs by maximal severity, AEs by relationship to study drug, AEs leading to treatment discontinuation, and AEs resulting in death by treatment arm for the Safety population. In addition, overall TEAEs and the number and percentage of subjects who experienced at least one TEAE, ocular TEAEs, non-ocular TEAEs, TE-SAEs, TEAEs by

maximal severity, TEAEs by relationship to study drug, TEAEs leading to treatment discontinuation, and TEAEs resulting in death by treatment arm for the Safety population.

Separate summaries will be provided for the following categories of AEs:

- Ocular AEs by SOC and PT
- Non-ocular AEs by SOC and PT
- Ocular TEAEs by SOC and PT
- Non-ocular TEAEs by SOC and PT
- Ocular TEAEs by SOC, PT, and maximal severity
- Non-ocular TEAEs by SOC, PT, and maximal severity
- Ocular TEAEs by SOC, PT, and strongest relationship to study drug
- Non-ocular TEAEs by SOC, PT, and strongest relationship to study drug
- Ocular TEAEs by SOC, PT, maximal severity, and strongest relationship to study drug
- Non-ocular TEAEs by SOC, PT, maximal severity, and strongest relationship to study drug
- TEAEs That Led to Premature Discontinuation
- SAEs

Adverse Events and TEAEs will be summarized using discrete summary statistics and presented by treatment arm and all subjects for the the Safety population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

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.

Subjects experiencing more than one AE within a given SOC or PT are counted once within that SOC or PT for the maximal severity.

The relationship of each AE to the study drug should be determined by the investigator using these explanations:

- Definitely Related: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
- Probably Related: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- Possibly Related: Relationship exists when the AE follows a reasonable sequence from the time of administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- Unlikely to be related: Relationship between the AE and IP is more than likely to be unrelated to IP administration but the relationship cannot be definitely attributed to another cause.
- Not Related: Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, OR exposure to IP has not occurred.

Subjects experiencing more than one AE within a given SOC or PT are counted once within that SOC or PT for the maximum relationship. All AEs, ocular AEs, non-ocular AEs, and SAEs will be presented in subject listings.

15.2 Visual Acuity (ETDRS)

The logarithm of the minimum angle of resolution (logMAR) VA [redacted]. A subject listing of VA will also be produced.

15.3 Slit-Lamp Biomicroscopy Examination

Slit lamp biomicroscopic observations will be graded [redacted]

- [redacted]

[redacted] A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

15.4 Intraocular Pressure

Intraocular pressure will be measured [redacted]

[redacted] A subject listing of IOP will also be produced.

15.5 Dilated Fundoscopy Examination

Dilated fundus exams will be performed [redacted]

[redacted] A subject listing of the dilated fundoscopy parameters will also be produced.

16. Changes from Protocol-Stated Analyses

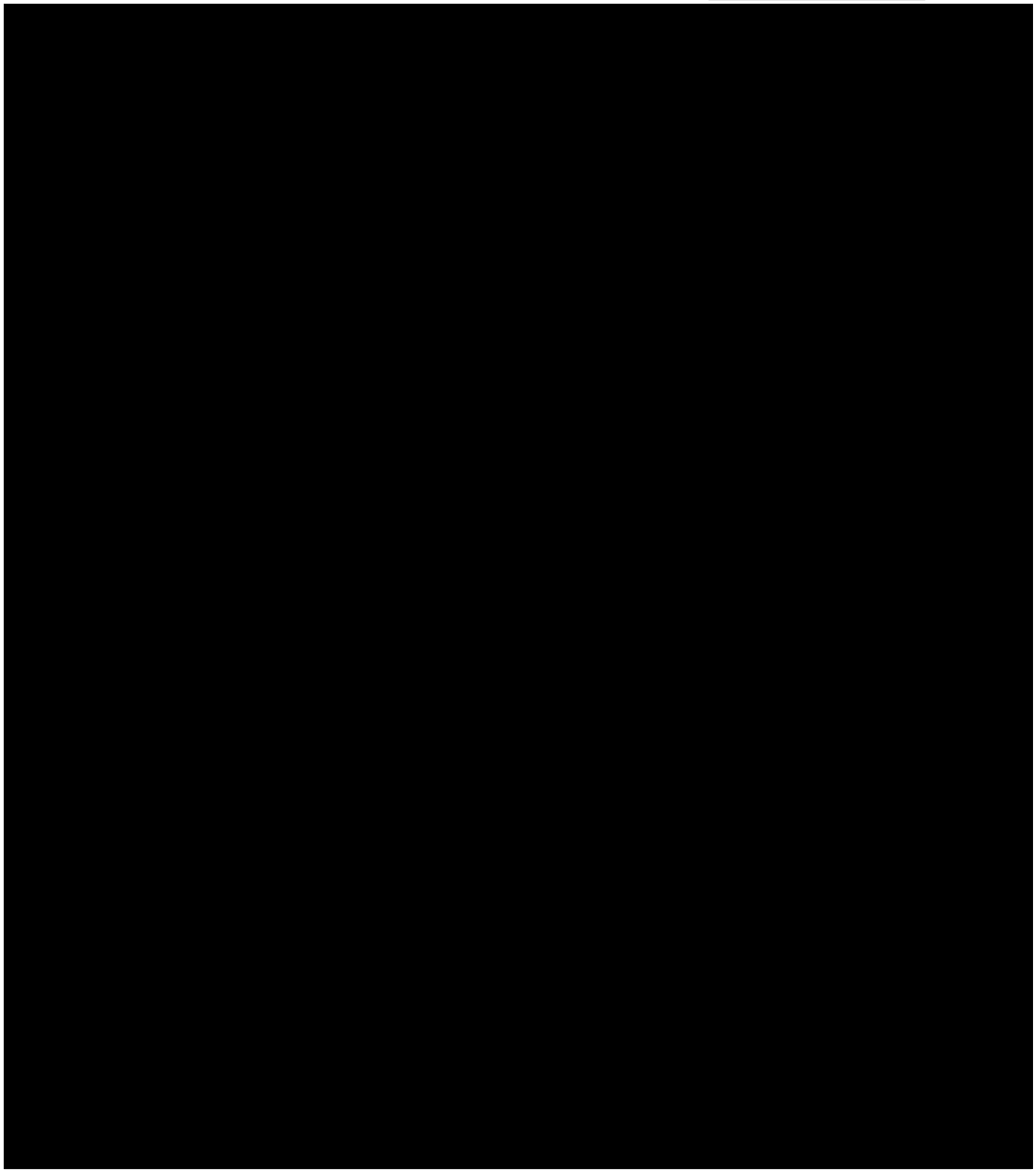
[redacted]

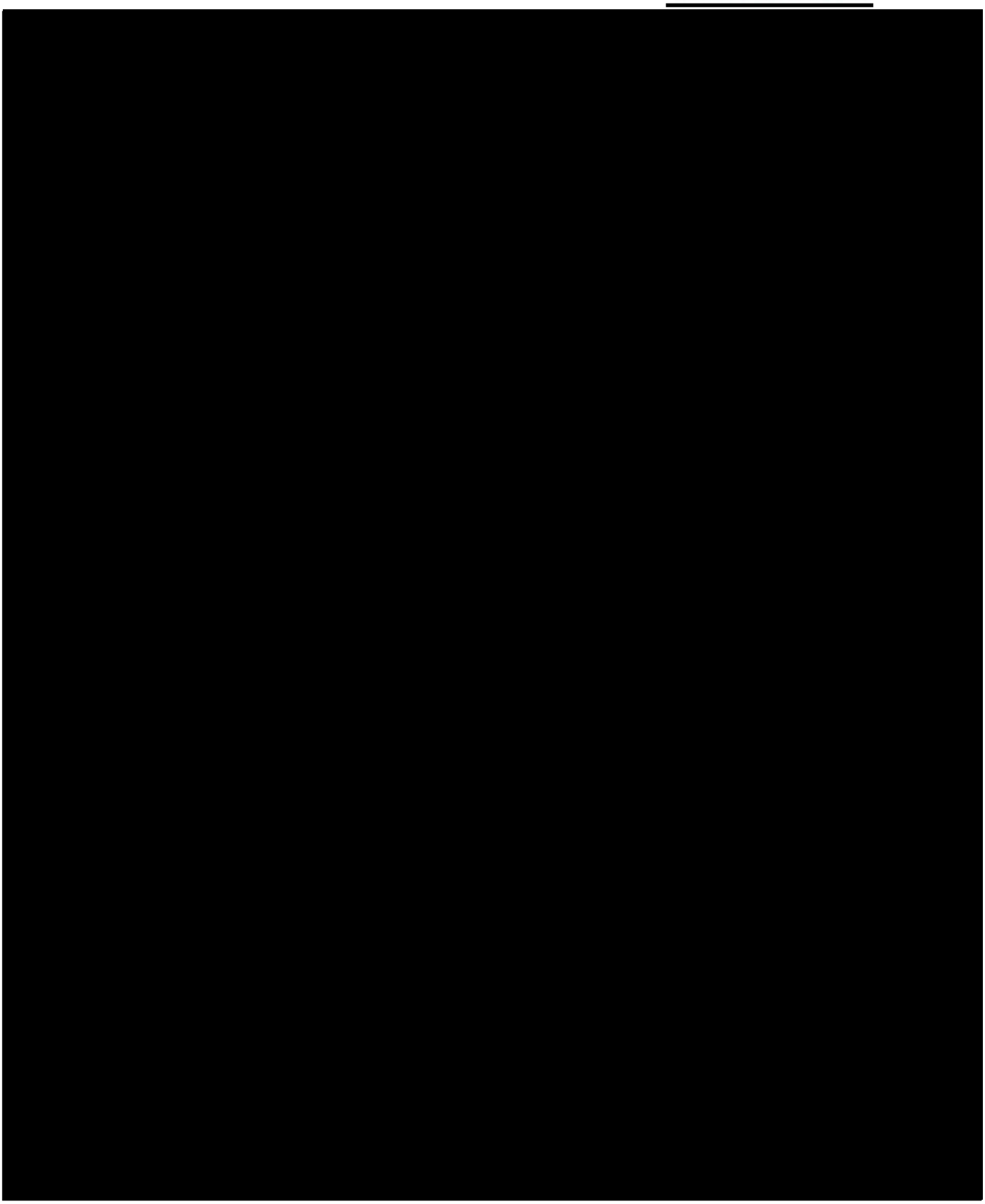
17. Revision History

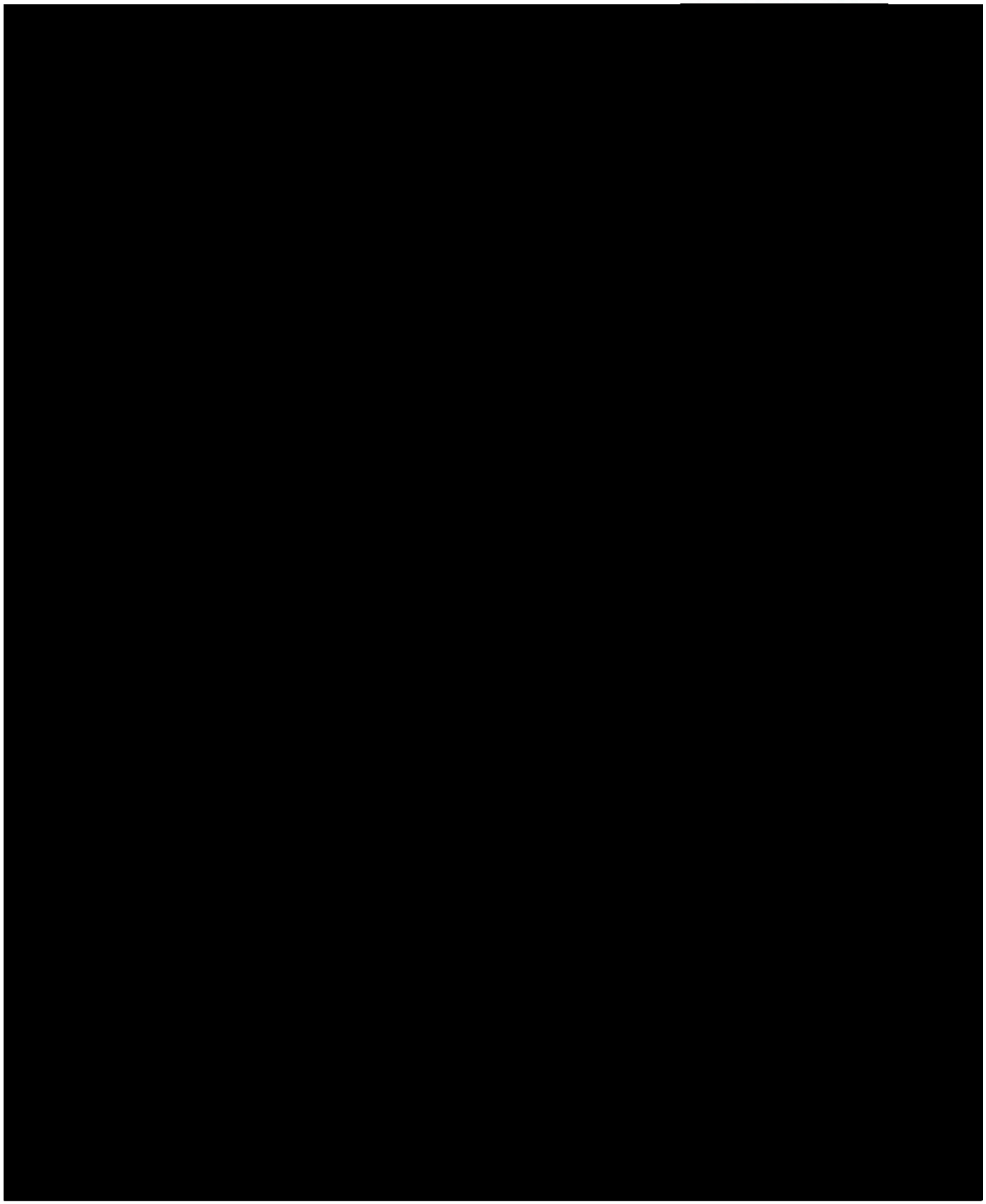
[redacted]

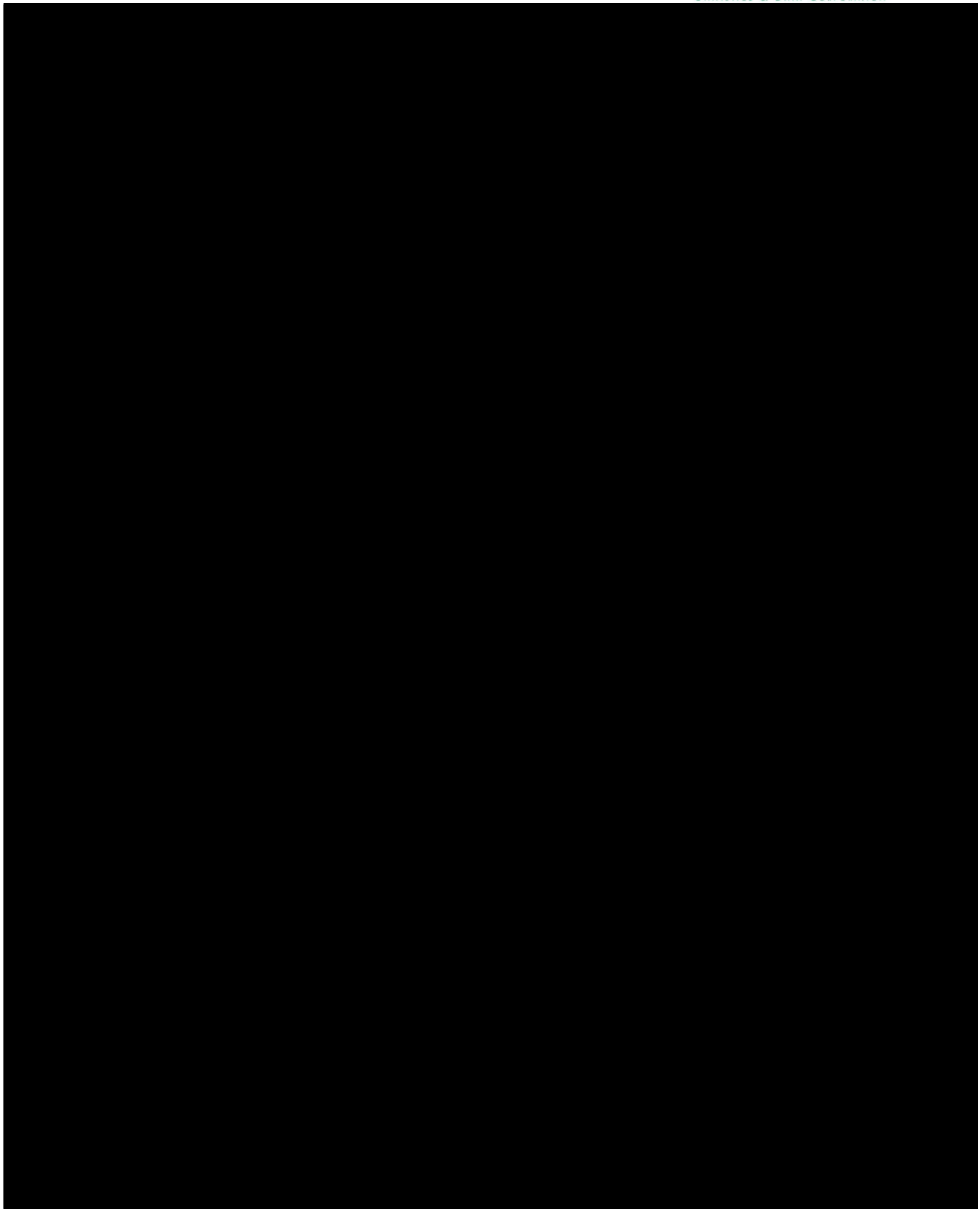
[redacted]

[redacted]









[redacted]

19. Listings

[redacted]