STATISTICAL ANALYSIS PLAN

A Phase 3, Multi-Center, Randomized, Double-Masked, Vehicle-Controlled Clinical Study to Assess the Safety and Efficacy of 1% Tavilermide and 5% Tavilermide Ophthalmic Solutions for the Treatment of Dry Eye

Sponsor: Mimetogen Pharmaceuticals USA, Inc.

Protocol Number: MIM-728

NCT Number (NCT03925727)

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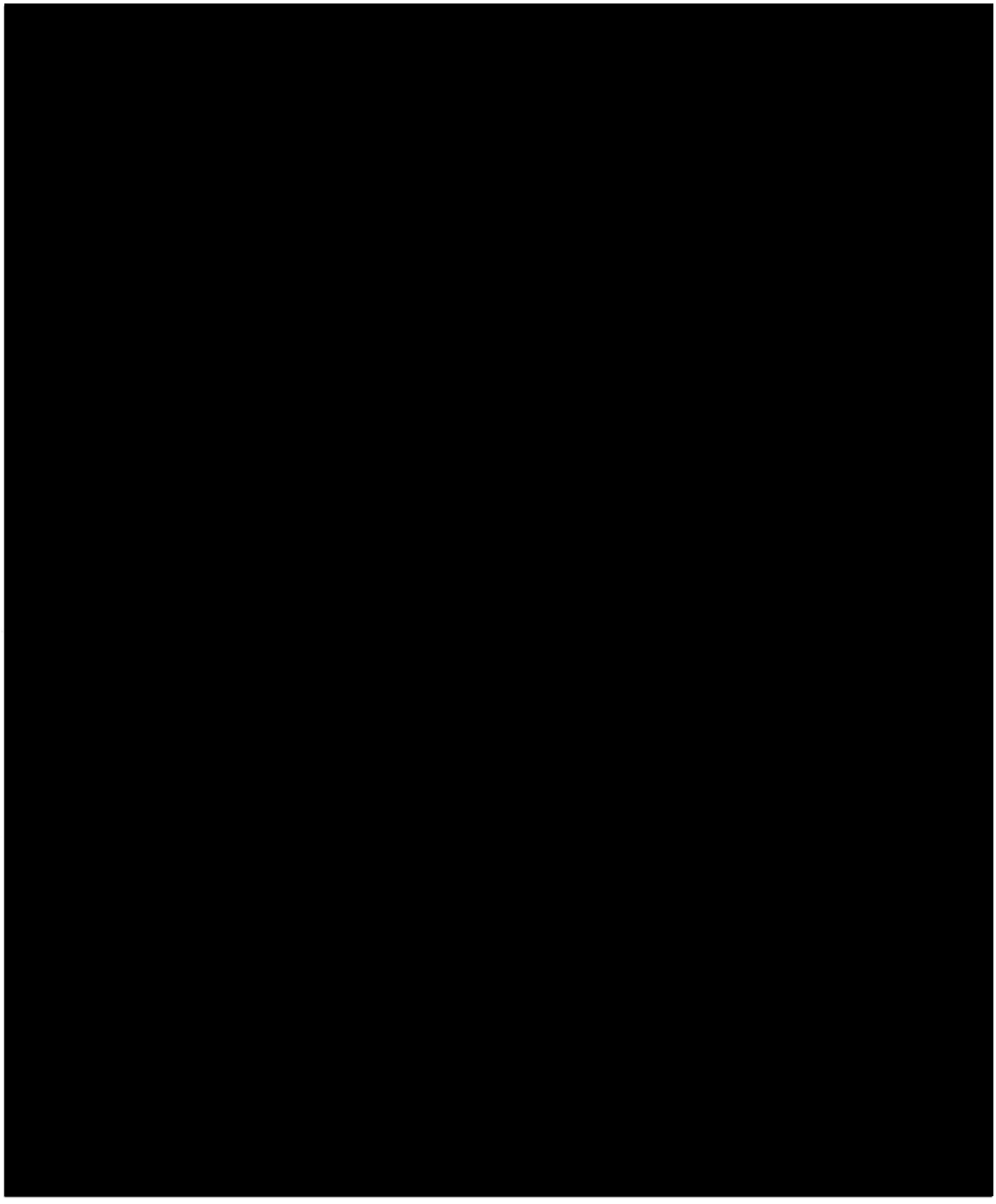

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BID	Bis in die (Twice Daily)
CFS	Corneal Fluorescein Staining
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS	Eye Dryness Score
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LS	Least Squares
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
NCS	Not Clinically Significant

NEI	National Eye Institute
ODO	Observed Data Only
OU	Both Eyes
PDF	Portable Document Format
PMM	Pattern Mixture Model
PP	Per Protocol
PT	Preferred Term
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
TEAE	Treatment-Emergent Adverse Event
TE-SAE	Treatment-Emergent Serious Adverse Event
TFBUT	Tear Film Break-Up Time
TMF	Trial Master File
TOP	Topically
VAS	Visual Analog Scale
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol MIM-728, version 2.0 dated 03-JUL-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

The primary objective of the study is to compare the efficacy and safety of 5% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of Dry Eye Disease (DED).

The secondary objective of the study is to compare the efficacy and safety of 1% tavilermide ophthalmic solution to placebo for the treatment of the symptoms and signs of DED.

2.1 Primary Endpoints

The primary efficacy endpoints are:

- Change from baseline in the Eye Dryness Score (EDS) at Visit 6 (Day 85) [redacted]
- Change from baseline in total corneal fluorescein staining (CFS) score at Visit 6 (Day 85) [redacted].

2.2 Key Secondary Endpoints

The key secondary efficacy endpoints are:

- Change from baseline in the EDS at Visit 4 (Day 29) [redacted];
- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]
- Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
- Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]
- Change from baseline in the EDS at Visit 4 (Day 29) [redacted]
- Change from baseline in total CFS at Visit 4 (Day 29) [redacted]

2.3 Other Secondary Endpoints

Other secondary endpoints will be compared between treatment groups: 5% tavilermide ophthalmic solution to placebo, 1% tavilermide ophthalmic solution to placebo, and 5% tavilermide ophthalmic solution to 1% tavilermide ophthalmic solution. The other secondary endpoints include the following:

- Eye dryness, discomfort, grittiness, pain, blurred vision, and photophobia [redacted]
- Frequency, severity, and total score [redacted]

- [redacted] at Visits 3 (Day 15), 4 (Day 29), 5 (Day 57), and 6 (Day 85), and the [redacted] at Visits 3 (Day 15), 4 (Day 29), 5 (Day 57), and 6 (Day 85);
- CFS in the inferior, superior, central, temporal, and nasal regions, and total corneal (i.e., sum of all regions) [redacted]
- Conjunctival lissamine green staining in the temporal, superior temporal, inferior temporal, superior nasal, inferior nasal, and nasal regions, and total conjunctival (i.e., sum of all regions) [redacted]
- [redacted] at Visit 6 (Day 85) and the [redacted] (Visit 1 [Day -14]) at Visit 6 (Day 85).

2.4 Safety Variables

The safety variables are:

- Incidence and severity of ocular Adverse Events (AE);
- Incidence and severity of non-ocular AEs;
- Concomitant medication monitoring/review;
- Visual acuity (Early Treatment of Diabetic Retinopathy Study [ETDRS]) at all visits;
- Slit-lamp biomicroscopy at all visits;
- Intraocular Pressure (IOP) at Visits 1 (Day -14) and 6 (Day 85);
- Dilated fundoscopy at Visits 1 (Day -14) and 6 (Day 85); and
- Ora Calibra® Drop Comfort Scale and Questionnaire at Visits 2 (Day 1) and 5 (Day 57).

2.5 Statistical Hypotheses

2.5.1 Primary Endpoints:

[redacted]

2.5.2 Key Secondary Endpoints:

[redacted]

[redacted]

[redacted]

3. Study Design and Procedures

3.1 General Study Design

This Phase 3 trial is a multi-center, double-masked, randomized, vehicle-controlled, parallel-group clinical study. There will be two active treatment groups, 1% tavilermide ophthalmic solution and 5% tavilermide ophthalmic solution, and one control group, placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution).

A subject's participation is to start with screening at Visit 1 (Day -14). If the subject is considered eligible for the study at the end of Visit 1 (Day -14), the subject will participate in a 14-day run-in period. Isotonic ophthalmic solution – also known as placebo ophthalmic solution (vehicle of tavilermide ophthalmic solution) – is the designated run-in and is to be administered to both eyes (OU), topically (TOP), and twice per day (BID) throughout the run-in period.

Baseline efficacy measurements are to be obtained at Visit 2 (Day 1). Should a subject qualify for final study entry at the end of Visit 2 (Day 1), [redacted]

- [redacted]
- [redacted]
- [redacted]

During the treatment period, the subject is to dose with their assigned treatment OU, TOP, and BID for approximately 85 days.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. 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:

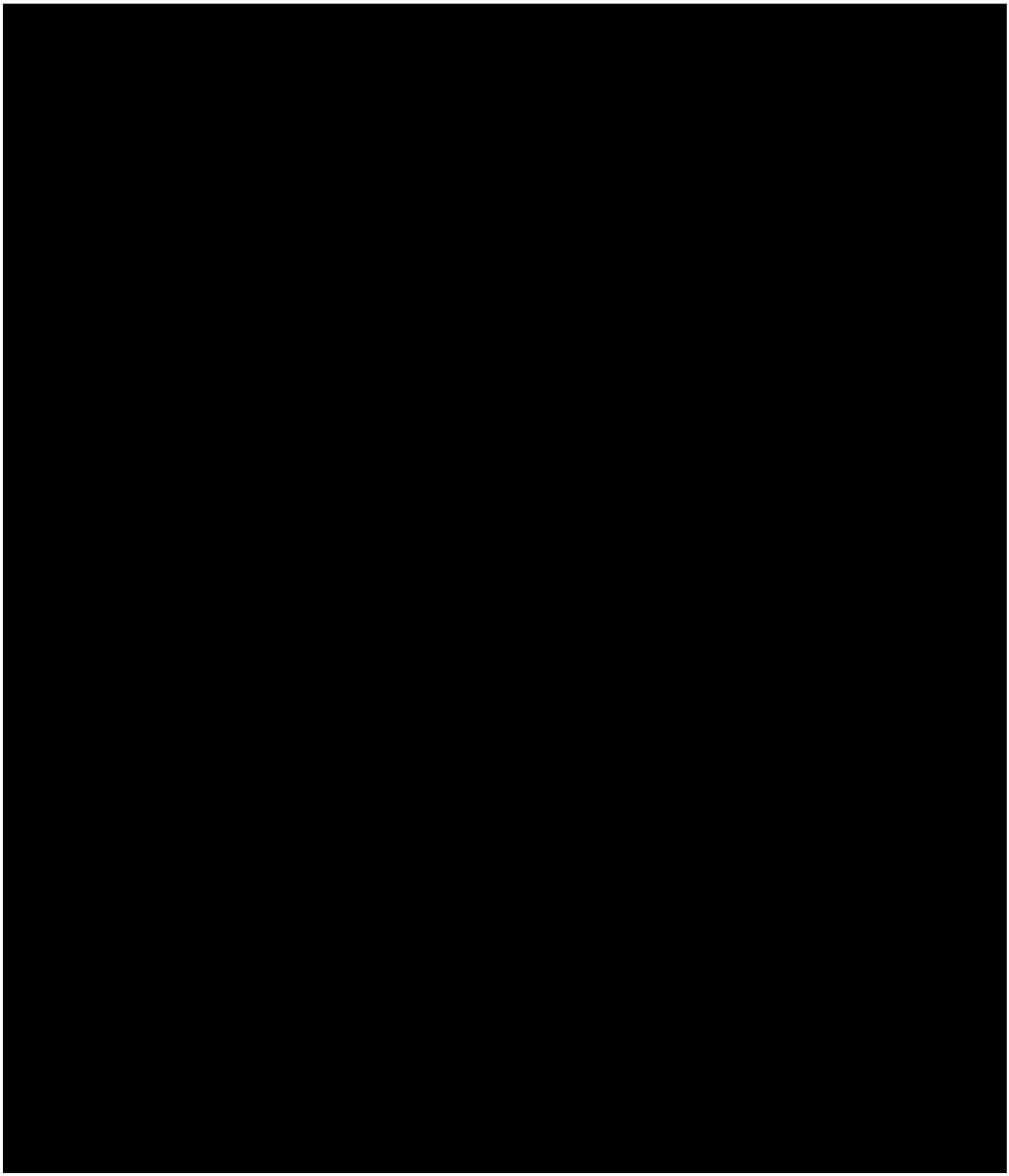
Table 1. Scheduled Visits, Planned Study Days, and Visit Windows

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

3.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Table 2.

Table 2. Schedule of Visits and Assessments



[redacted]

4. Study Treatments

4.1 Method of Assigning Subjects to Treatment Groups

A patient who meets all of the inclusion criteria and none of the exclusion criteria is eligible for randomization at Visit 2 (Day 1). [redacted]

[redacted]

A statistician not directly involved in the analysis of the study results will prepare the randomization schedule using block randomization to maintain balance between treatment groups. Randomization is to be done in a [redacted] respectively, by the interactive response technology (IRT) system.

Subjects are to be stratified by site and EDS as measured by the VAS at Visit 2 (Day 1) using the following strata:

[redacted]

Details required for stratification are to be entered into the IRT which will randomize the subject and assign a randomization number. Randomization numbers are to be four digits and will associate a subject to their assigned treatment group. The IRT will allocate a subject to treatment kits containing their randomized treatment; each treatment kit is identifiable by a five-digit kit number. The randomization number and all treatment kit numbers are to be recorded on the subject's source document and the appropriate electronic case report forms (eCRF). At Visits 2

(Day 1) and 3 (Day 15), each eligible subject is to receive one kit of their randomly assigned treatment. At Visits 4 (Day 29) and 5 (Day 57), each eligible subject is to receive two kits of their randomly assigned treatment.

4.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments.

The discrepancies in visual appearance among the investigational product (IP) mandate that there is at least one technician designated as unmasked at each clinical site. Once open, a treatment kit is to be handled by only the subject to which it was assigned and unmasked designees.

Unmasked technicians are uniquely delegated for facilitating the in-office dose and drop comfort assessments and performing randomized treatment kit accountability. Unmasked technicians may not participate in any other aspect of the trial that has a bearing on trial efficacy including symptom questionnaires, scribing for the Investigator, and data transcription. Unmasked technicians are not to have access to the electronic data capture (EDC) system. Clinical trial monitors who are designated as unmasked are to be responsible for reviewing randomized IP accountability. After unmasking, a clinical trial monitor is not to participate in other aspects of trial monitoring.

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.

If the Investigator identifies a medical need for unmasking the assigned treatment of a subject, they should, if possible, contact Ora and/or the Medical Monitor before completing the unmasking. Ora is to ask the site to complete the appropriate parts of the Unmasking Request Form and then to return the form. After receiving the form, Ora is to notify Mimetogen, and jointly they are to determine whether to approve the unmasking; Ora or Mimetogen may consult with the Medical Monitor as needed during this process. The result of the request is to be documented on the Unmasking Request Form.

If the request to unmask a subject is approved, the Investigator is to be provided the approval in writing via the Unmasking Request Form. The Investigator is to unmask the subject using the IRT and complete the Unmasking Memo. The Unmasking Memo is to be filed with the subject's study file, and a copy is to be sent to project management so that it may be included in the Trial Master File (TMF). For each unmasking request, the reason for the request, the date of the request, and the name and signature of the individual unmasking the subject are to be noted in the subject's study file.

5. Sample Size and Power Considerations

Approximately 1034 subjects are to be screened to enroll approximately 600 subjects at 15 to 20 sites. Subjects are to be randomized [redacted] to one of the three treatment groups as indicated below:

1. 250 subjects to 5% tavilermide ophthalmic solution,
2. 100 subjects to 1% tavilermide ophthalmic solution, and
3. 250 subjects to placebo ophthalmic solution.

Subjects are to be stratified by site and EDS as measured by the VAS at Visit 2 (Day 1) using the following strata:

[redacted]

Power calculations conservatively account for missing data; however, the primary analysis will impute missing data for all subjects. Assuming a 10% drop out rate, 225 subjects are expected to complete the study in each of the 5% tavilermide and placebo arms. [redacted]

6. Data Preparation

Electronic Case Report Forms will be developed by Statistics & Data Corporation, Incorporated (SDC). Data from source documents will be entered into the eCRF by site personnel. All users will complete role-based system and study-specific eCRF training prior to receiving access to the study database. User access will be granted based on a user's role in the study and will be controlled through individual login credentials including a unique User ID and password.

The clinical study database will be developed and tested in iMedNet™ v1.183.4 or higher. iMedNet™ is delivered as a single-instance multi-tenant Software-as-a-Service (SaaS) EDC system and is developed, maintained, and hosted by MedNet Solutions located in Minnetonka, Minnesota. Therefore, over the duration of the study, MedNet Solutions may apply system updates to the EDC system as part of their continuous improvement efforts.

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 Mimetogen and Ora in consultation with SDC.

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

- All data management requirements are met according to SDC standard operating procedures (SOP), including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC, Mimetogen and Ora personnel.
- Protocol deviations have been identified and status defined (major/minor deviations).
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7. Analysis Populations

7.1 Intent-to-Treat

[redacted]

7.2 Modified Intent-to-Treat

[redacted]

[redacted]

7.3 Per Protocol

[redacted]

7.4 Safety

[redacted]

8. General Statistical Considerations

8.1 Unit of Analysis

[redacted]

8.2 Missing or Inconclusive Data Handling

The primary and key secondary efficacy analyses will use the ITT population with MCMC multiple imputation methodology under the assumption that data are missing at random. Additional sensitivity analyses will be performed using multiple imputation under the assumption that data are missing not at random using a control-based pattern mixture model (PMM), the last observation carried forward (LOCF) imputation method for missing data as well as using the observed data only on the ITT population. Further sensitivity analyses will include

MCMC imputation with the mITT population to examine the effect of COVID-19 related discontinuations and COVID-19 related significant protocol deviations. Additionally, the PP population with observed data only will be used to assess sensitivity.

No other secondary efficacy endpoints or safety endpoints will be imputed.

8.3 Definition of Baseline

Baseline measures are defined as the last measure prior to the initiation of study treatment. Change from baseline will be calculated as Follow-up Visit – Baseline Visit.

[redacted]

8.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, and visit (as applicable) based on all randomized subjects unless otherwise specified.

All summaries will be presented by treatment group and visit where appropriate, unless otherwise specified. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition. For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug dictionaries, as appropriate.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, maximum, and two-sided 95% confidence intervals (CI) for the mean. Minima and maxima will be reported with the same precision as the raw values; means, medians and confidence interval bounds will be presented to

one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment groups and placebo will be calculated as Active minus Placebo and change from baseline will be calculated as Follow-up Visit - Baseline. The baseline measure will be defined as the last non-missing measure prior to initiation of investigational treatment.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. CIs for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit.

8.5 Adjustments for Multiplicity

[redacted]

The hierarchical testing sequence will proceed as follows:

Primary Endpoints:

1. Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
2. Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]

[redacted]

Key Secondary Endpoints:

3. Change from baseline in the EDS at Visit 4 (Day 29) [redacted]
4. Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]
5. Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
6. Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]
7. Change from baseline in EDS at Visit 4 (Day 29) [redacted]
8. Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]

9. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects.

The total number of randomized subjects and the number of randomized subjects in each of the analysis populations (ITT, mITT, PP, and Safety) will be displayed by treatment. The number of randomized subjects in the ITT population + Site 88 will also be displayed by treatment. The ITT, mITT populations use treatment as randomized; PP and Safety populations use treatment as treated. Percentages are based on the total number of subjects randomized in each treatment group.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects who discontinued the study. The reasons for study discontinuation that will be summarized include: AE, protocol violation, administrative reasons, sponsor termination of study, subject choice, and other. COVID-19 related discontinuations will be summarized as well. A subject listing will be provided that includes the date of and reason for premature study discontinuation. COVID-19 related discontinuations will be summarized in a separate listing.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects. The protocol deviations that will be summarized include: Informed Consent, Inclusion / Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site, Improper Protocol Procedures at Site, Site's Failure to Report Severe Adverse Event (SAE) / AE, Visit Out of Window (missed, early, late), Subject's Non-compliance with Test Article, Subject's Use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. COVID-19 related protocol deviations will be summarized. A subject listing will be provided that includes the date of the deviation, the deviation code, the deviation description, and the classification of whether the deviation was

judged to be major or minor. COVID-19 related protocol deviations will be provided in a separate listing.

In addition, subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations, and exclusions from any analysis population. A listing of screen failure subjects will also be provided that includes screen failure date, visit of screen failure, reason for screen failure and date of dry eye diagnosis.

A subject listing of all subjects affected by COVID-19 will be generated.

10. Demographic and Pretreatment Variables

10.1 Demographic Variables

The demographic variables collected in this study include age, sex, ethnicity, race, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multiple. Demographic variables will be summarized for the ITT, mITT, PP, Safety populations, separately.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics. Age will also be categorized as follows: [redacted]. Age will be reported in years and calculated using the following formula:

[redacted]

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color by eye (OD and OS).

A subject listing that includes all demographic variables will be provided.

10.2 Pretreatment Variables

Baseline disease characteristics will be summarized for the ITT, mITT, PP, and Safety populations, separately by treatment group using continuous descriptive statistics for VAS ocular symptoms (eye dryness, discomfort, grittiness, pain, blurred vision, and photophobia), CFS (inferior, superior, central, temporal, nasal, and corneal regions), SANDE questionnaire (frequency, severity, and total), TFBUT, and conjunctival lissamine green staining.

Unanesthetized Schirmer's test for screening Visit 1 (Day -14) will also be summarized using continuous descriptive statistics. Discrete summary statistics will be used to summarize visual acuity and IOP at screening Visit 1 (Day -14). Discrete summary statistics will also be used to summarize slit-lamp biomicroscopy, dilated fundoscopy, and Ora Calibra® Drop Comfort Scale and Questionnaire at baseline. For assessments by eye, separate summaries will be presented for the study eye and fellow eye.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be coded using MedDRA version 22.0.

Ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Non-ocular medical history will be similarly summarized at the subject and event level. 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.

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

11.2 Concomitant Medications

Concomitant medications will be coded using WHO Drug Global B3 (March 2019) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name will be defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (eg, multivitamins) then the drug name will be summarized as the preferred name.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug. Prior medications are reported medications with a stop date prior to study drug administration.

Concomitant medications will be summarized separately using the Safety and ITT populations, and separately for ocular and non-ocular medications. Medications will be tabulated for each treatment group using frequencies and percentages. Prior medications will be provided in subject listings with concomitant medications, but will not be summarized. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant and prior medications will be generated separately for ocular and non-ocular medications.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Dosing compliance will be based off of the unused vial count. [redacted]

Dosing compliance (% compliance) will be assessed by calculating the number of actual vials used and comparing that to the expected number of used vials as follows:

[redacted]

The number of doses taken will be calculated from

[redacted]

recorded in the eCRF. The expected number of used vials that will be used for calculating compliance will be calculated as:

[redacted]

for all subjects. If a randomized subject discontinues from the study on Day 1, the number of expected doses will be 1.

A categorical dosing compliance variable will also be derived as non-compliant [redacted], compliant [redacted] and over compliant [redacted]

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the ITT population. The compliance category defined above will be summarized with discrete summary statistics.

Subject listing of dosing compliance, study drug accountability, and study drug instillation will also be produced.

12.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

[redacted]

If a randomized subject discontinues from the study on Day 1, the extent of exposure will be 1.
Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

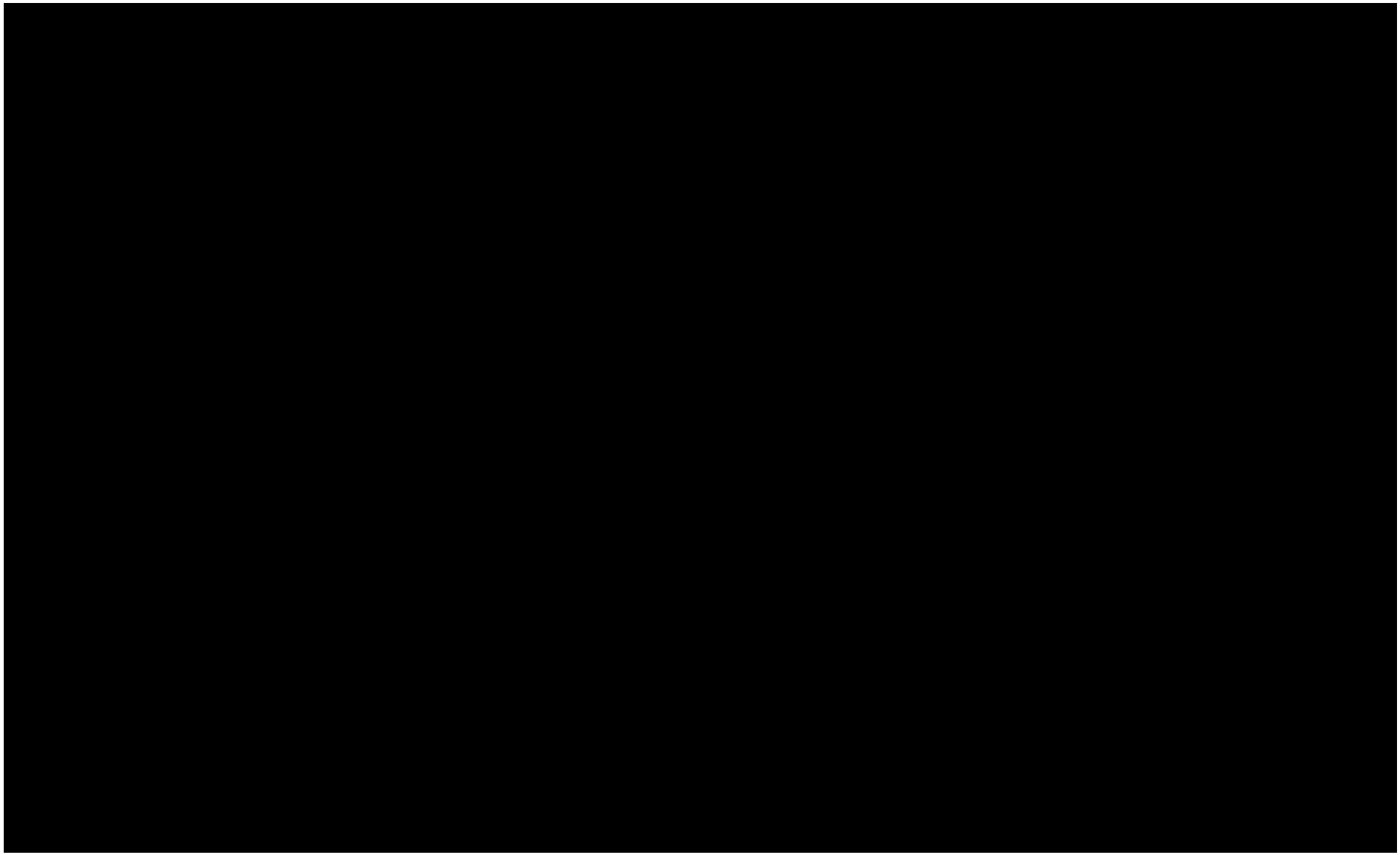
[redacted]

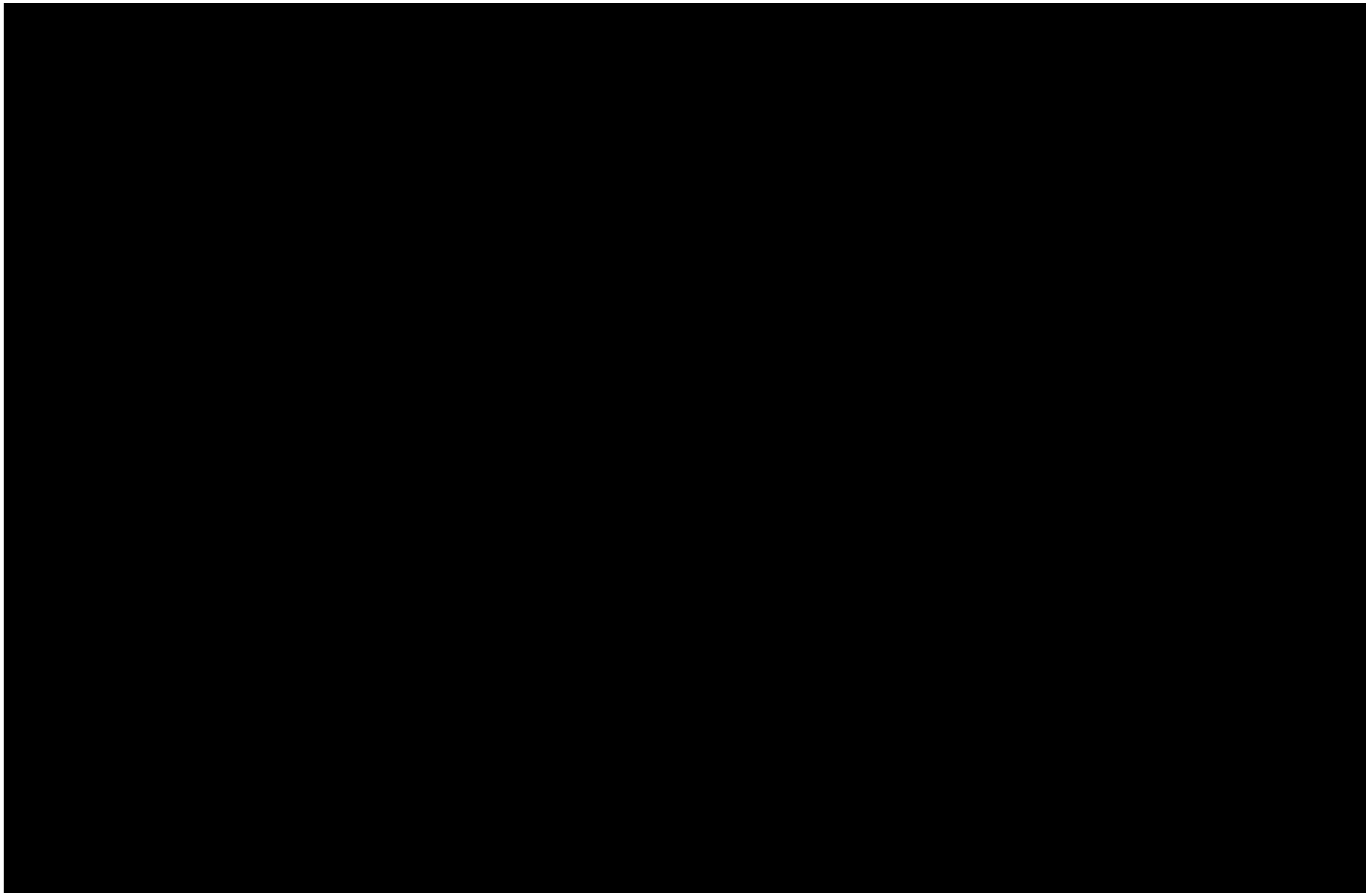
Extent of treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group using the Safety population. A subject listing of treatment exposure will also be produced.

13. Efficacy Analyses

The following table presents a summary of the primary, key secondary, and secondary efficacy analyses that will be performed for this study.

Analyses of the Primary, Key Secondary and Secondary Efficacy Variables





13.1 Primary Efficacy Analysis

The primary efficacy endpoints of the study are:

- Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
- Change from baseline in total CFS at Visit 6 (Day 85) [redacted]

[redacted]

13.1.1 EDS AT VISIT 6 (DAY 85), 5% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

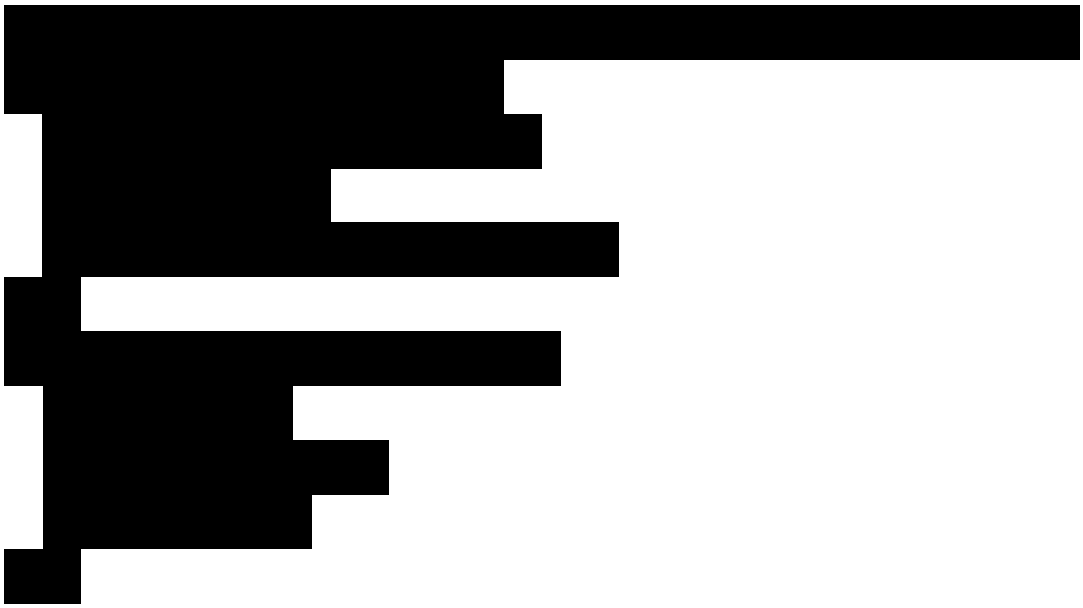
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

13.1.2 TOTAL CFS AT VISIT 6 (DAY 85), 5% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

13.2 Key Secondary Efficacy Analyses

The following are key secondary endpoints:

- Change from baseline in the EDS at Visit 4 (Day 29) [redacted]

- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]
- Change from baseline in the EDS at Visit 6 (Day 85) [redacted]
- Change from baseline in total CFS score at Visit 6 (Day 85) [redacted]
- Change from baseline in the EDS at Visit 4 (Day 29) [redacted]
- Change from baseline in total CFS score at Visit 4 (Day 29) [redacted]

13.2.1 EDS AT VISIT 4 (DAY 29), 5% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

13.2.2 TOTAL CFS AT VISIT 4 (DAY 29), 5% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

13.2.3 EDS AT VISIT 6 (DAY 85), 1% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

13.2.4 TOTAL CFS AT VISIT 6 (DAY 85), 1% TAVILERMIDE VS PLACEBO

[redacted]

[redacted]

13.2.5 EDS AT VISIT 4 (DAY 29), 1% TAVILERMIDE VS. PLACEBO

[redacted]

[redacted]

13.2.6 TOTAL CFS AT VISIT 4 (DAY 29), 1% TAVILERMIDE VS. PLACEBO

[redacted]

[redacted]

13.3 Other Secondary Efficacy Analyses

[redacted]

The following other secondary efficacy endpoints will be tested:

- Eye dryness, discomfort, grittiness, pain, blurred vision, and photophobia [redacted]
- Frequency, severity, and total score [redacted]
- [redacted]
- CFS in the inferior, superior, central, temporal, nasal, and corneal (i.e., sum of all regions) regions [redacted]
- Conjunctival lissamine green staining in the temporal, superior temporal, inferior temporal, superior nasal, inferior nasal, nasal, and conjunctival (i.e., sum of all regions) regions [redacted]
- [redacted]

13.3.1 VISUAL ANALOG SCALE

[redacted]

13.3.2 Symptom Assessment in Dry Eye Questionnaire

[redacted]

13.3.3 Tear Film Break-Up Time

[redacted]

[redacted]

13.3.4 CORNEAL FLUORESCEIN STAINING

[redacted]

[redacted]

13.3.5 CONJUNCTIVAL LISSAMINE GREEN STAINING

[redacted]

[redacted]

[redacted]

[redacted]

13.3.6 UNANESTHETIZED SCHIRMER'S TEST

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.4 Summary of Efficacy Analyses

[redacted]

14. Safety Analyses

[redacted]

14.1 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 a study drug, 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. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and

therapeutic parameters (e.g., energy applied, sizing, dose release, and anatomic fit) associated with medical device use. 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 of AEs, TEAEs, SAEs, and treatment-emergent serious adverse events (TE-SAE). The summary will also include the number and percentage of subjects withdrawn due to a TEAE, the number and percentage of subjects with a TEAE resulting in death, and the number and percentage of subjects who experienced at least one AE, TEAE, SAE and TE-SAE, by treatment group and for all subjects. This summary will include breakdowns of AEs further categorized as ocular or non-ocular.

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

- Ocular TEAEs
- Non-ocular TEAEs
- TEAEs that led to premature discontinuation
- TE-SAEs

Summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC) and preferred term (PT). TEAEs will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT). 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 study drug 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.

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

- **Suspected:** A reasonable possibility exists that the IP caused the AE. A suspected AE can be further defined as:
    - Definite: 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.
    - Probable: 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.
    - Possible: Relationship exists when the AE follows a reasonable sequence from the time of IP administration but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- **Not Suspected:** A reasonable possibility does not exist that the IP caused the AE.
    - 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.

Only suspected TEAEs are considered as treatment-related TEAEs.

[redacted]

All AEs will be presented in a subject listing. Listings of ocular AEs, non-ocular AEs, and all serious AEs will be presented in separate listings.

14.2 Visual Acuity (ETDRS)

[redacted]

14.3 Slit-Lamp Biomicroscopy

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

14.4 Dilated Fundoscopy

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

14.5 Intraocular Pressure

[redacted]

14.6 Ora Calibra® Drop Comfort Scale and Questionnaire

[redacted]

[redacted]

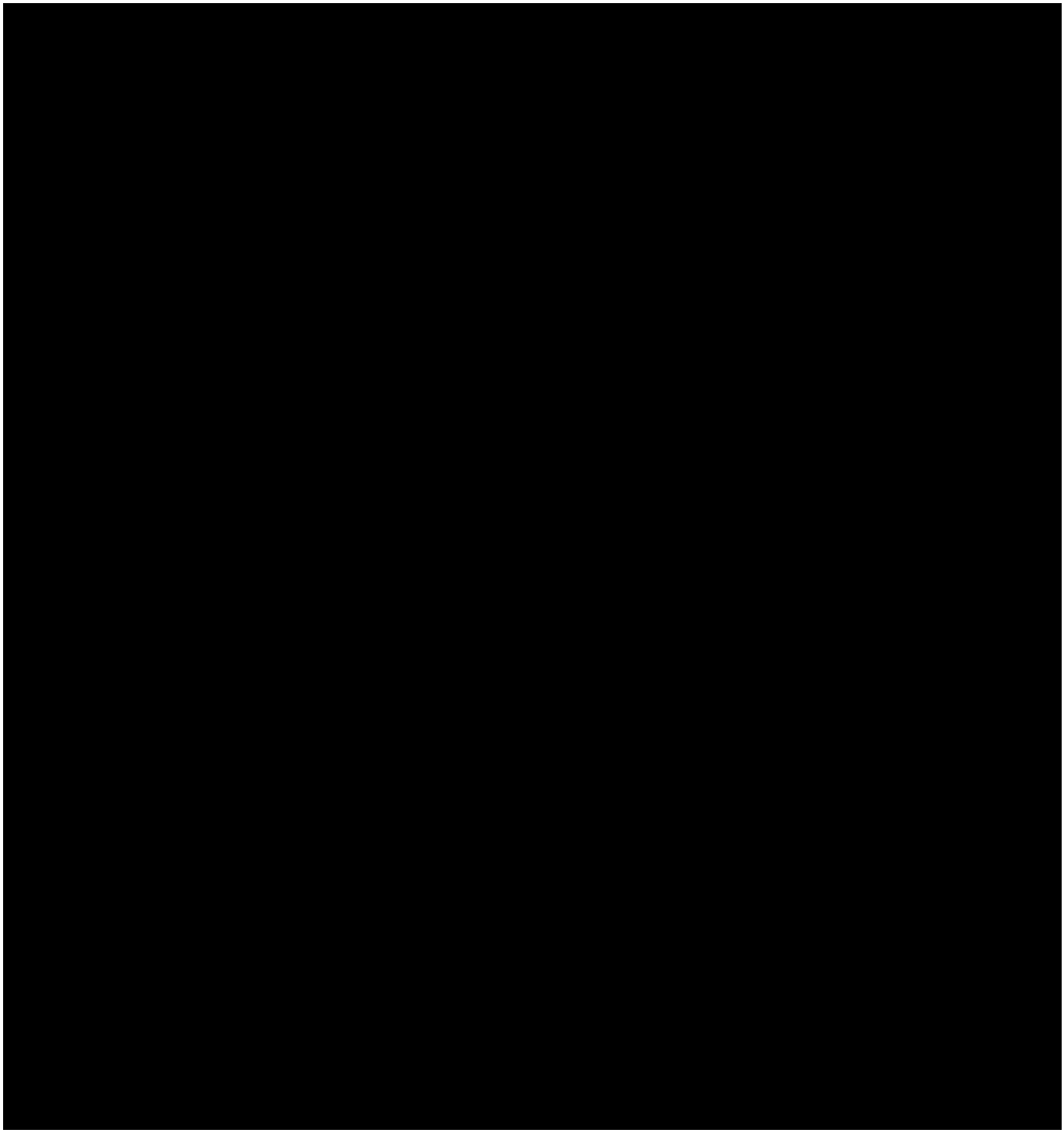
15. Interim Analyses

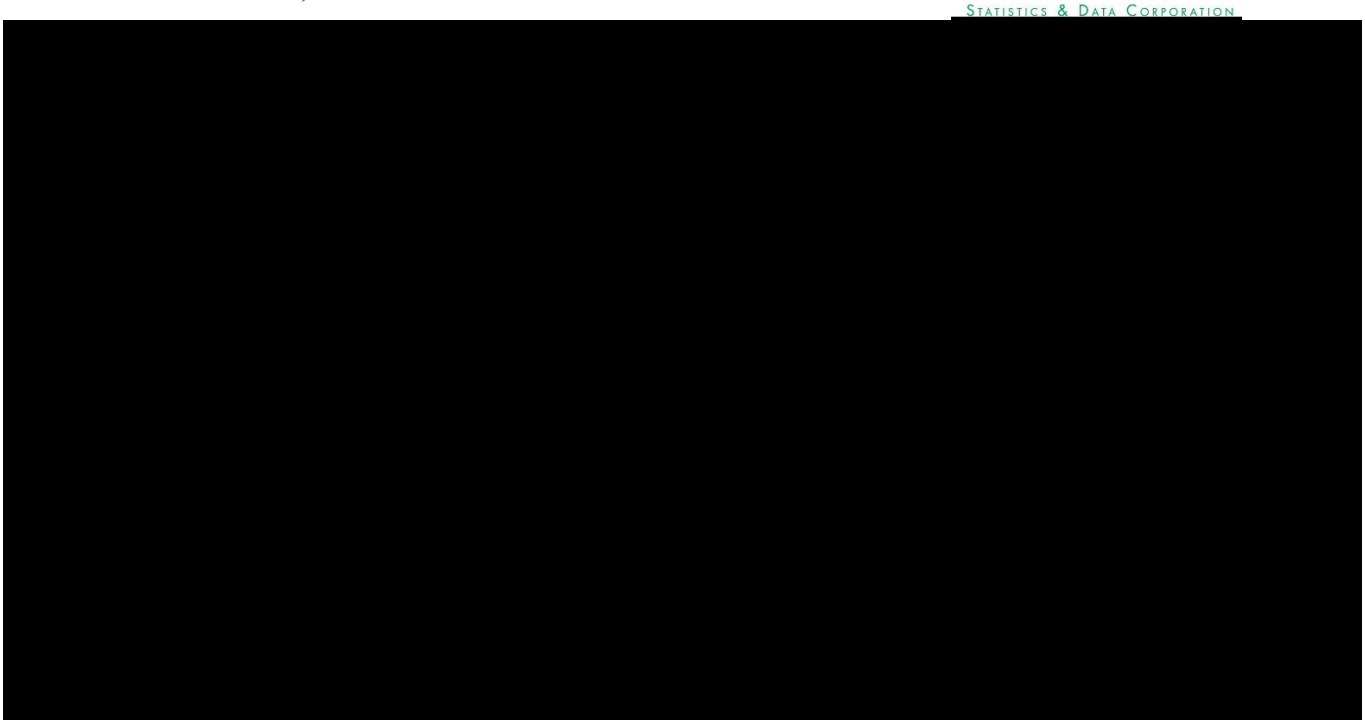
[redacted]

16. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

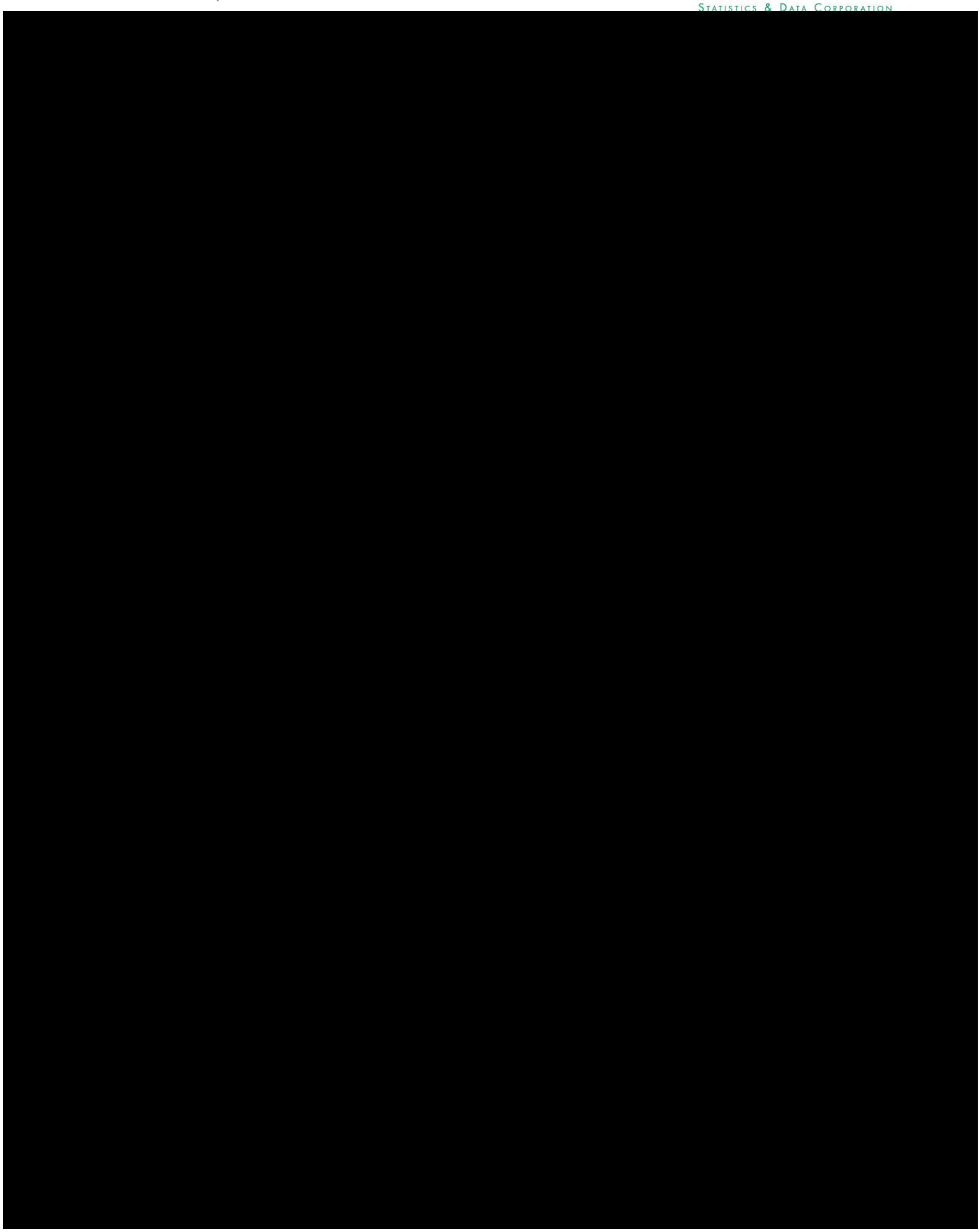
17. Revision History

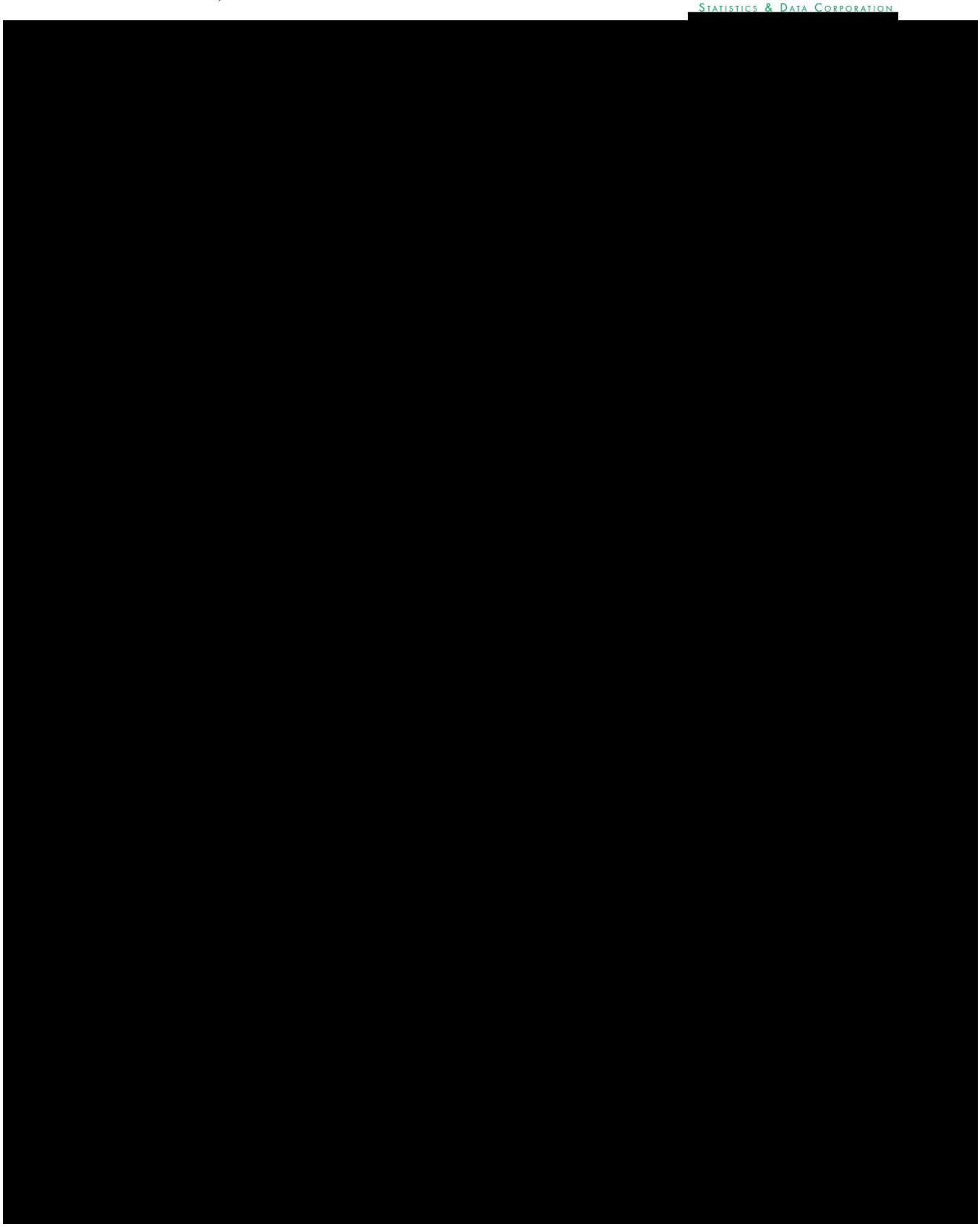


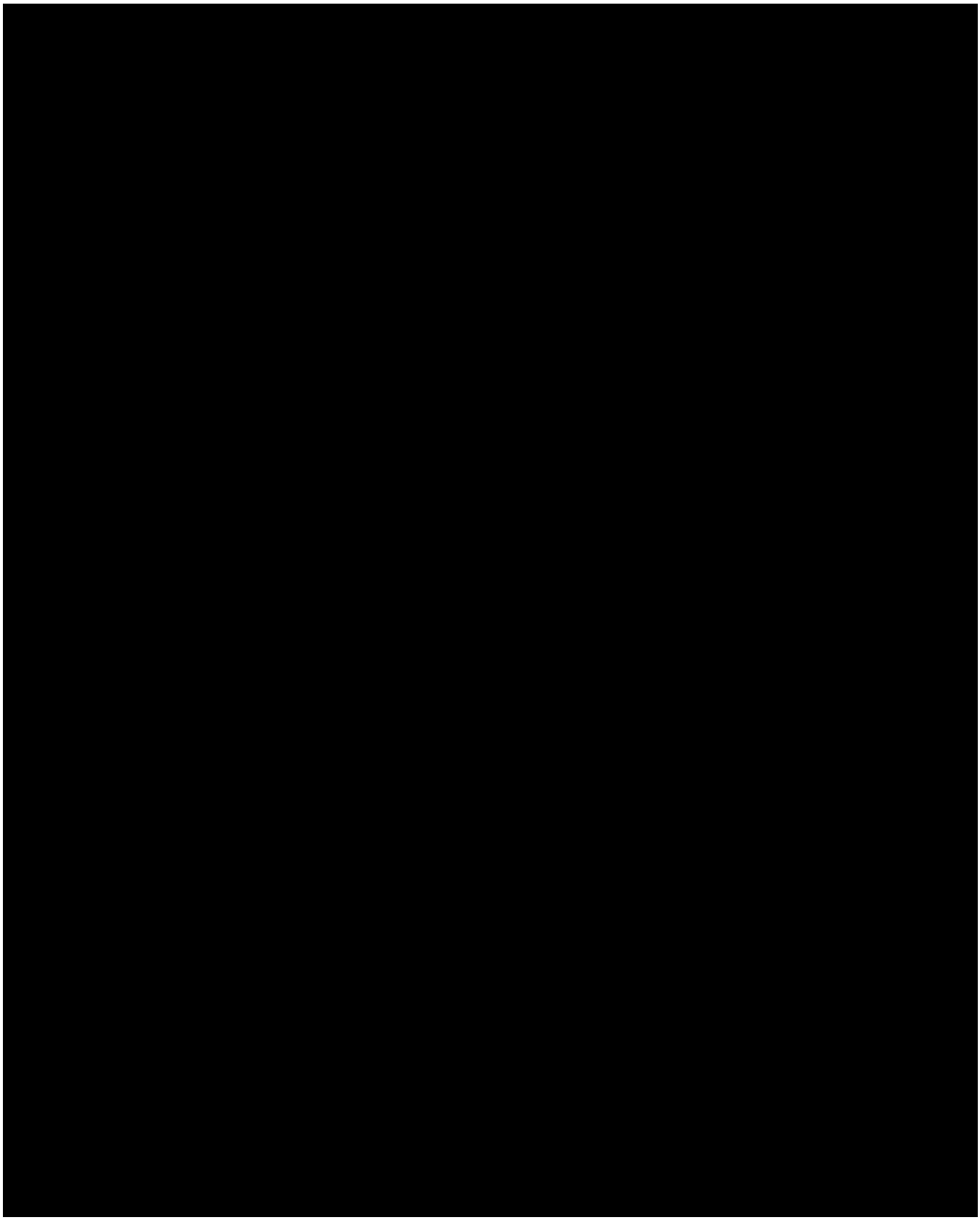


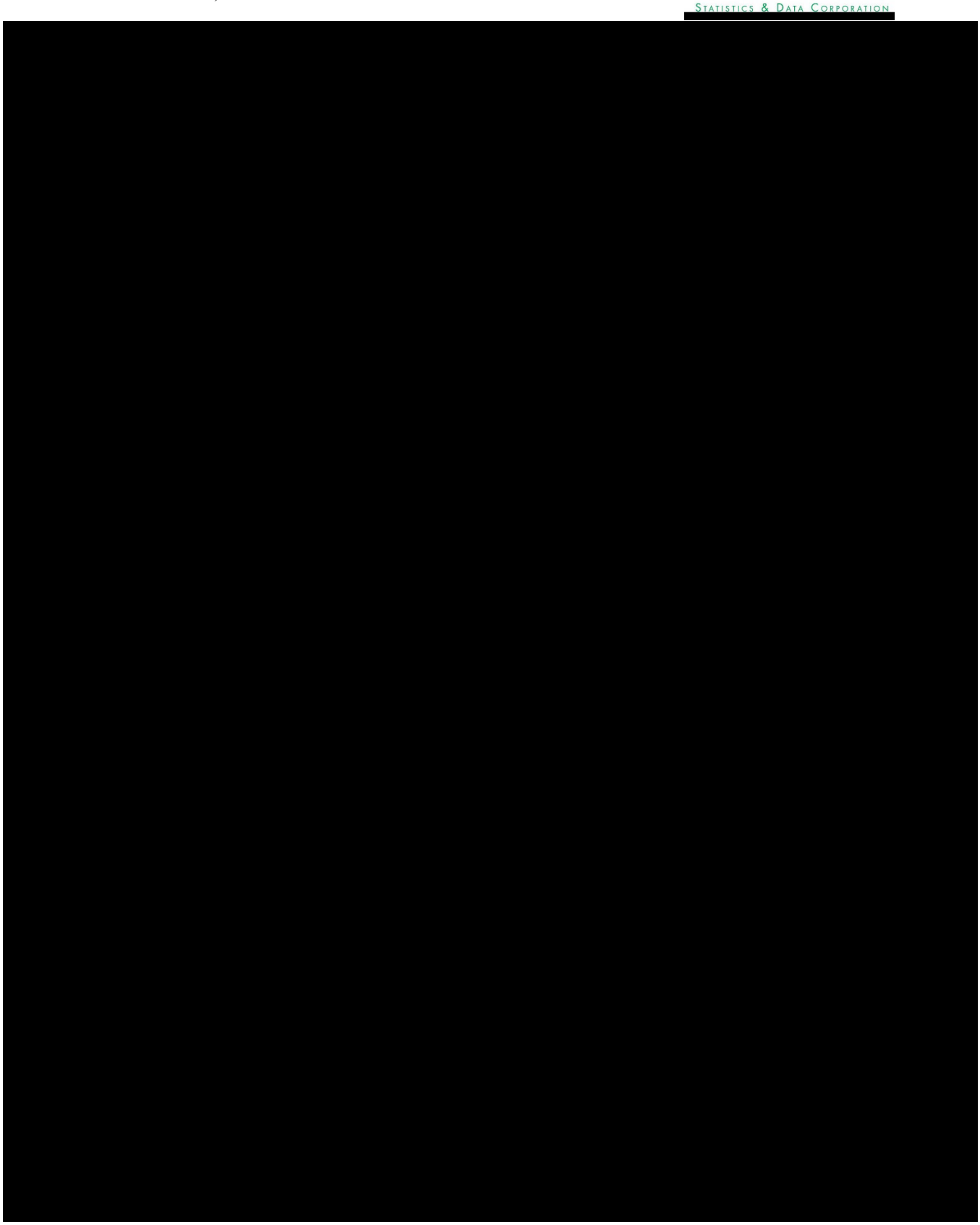
18. Tables

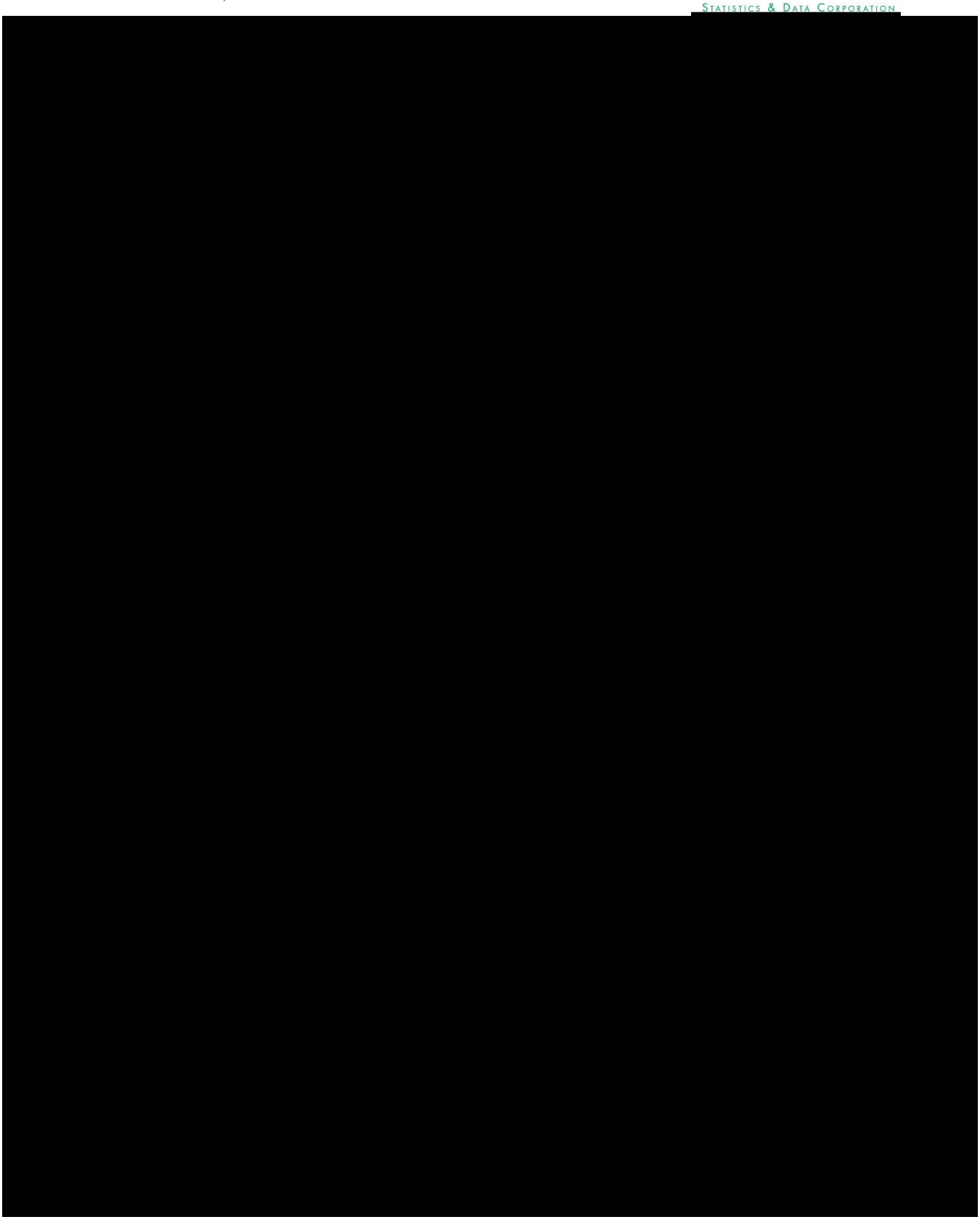
Tables that will be included in the topline delivery are shown in boldface font.











[redacted]

19. Listings

[redacted]