STATISTICAL ANALYSIS PLAN

A Phase 2 Multi-Center, Randomized, Double Masked, Placebo Controlled Study to Assess the Safety and Efficacy of ST-100 Ophthalmic Solution in Subjects Diagnosed with Dry Eye Disease

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Protocol Number: ST100-001

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Date: 25OCT2021

Version: 1.0

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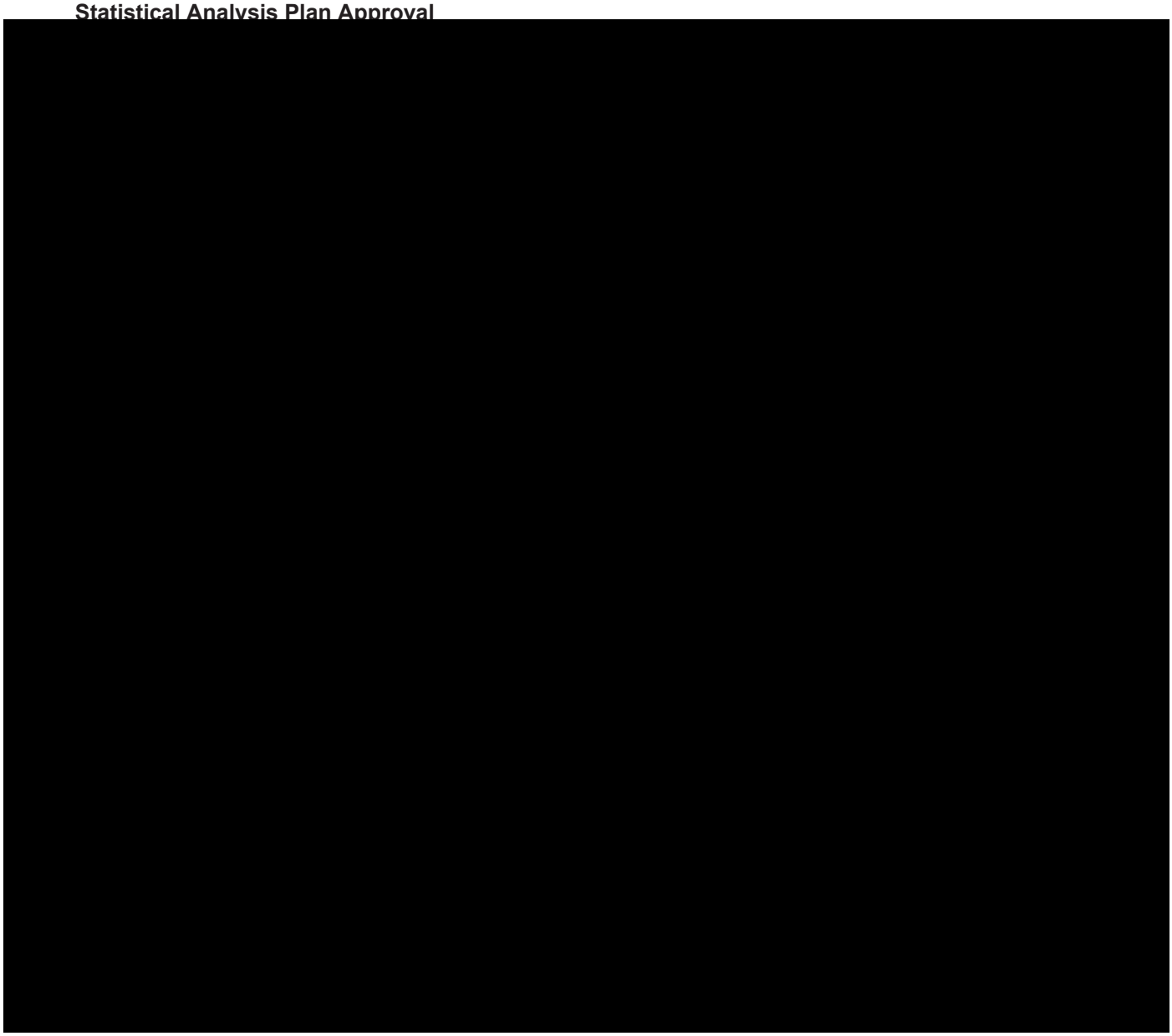
Statistical Analysis Plan Approval



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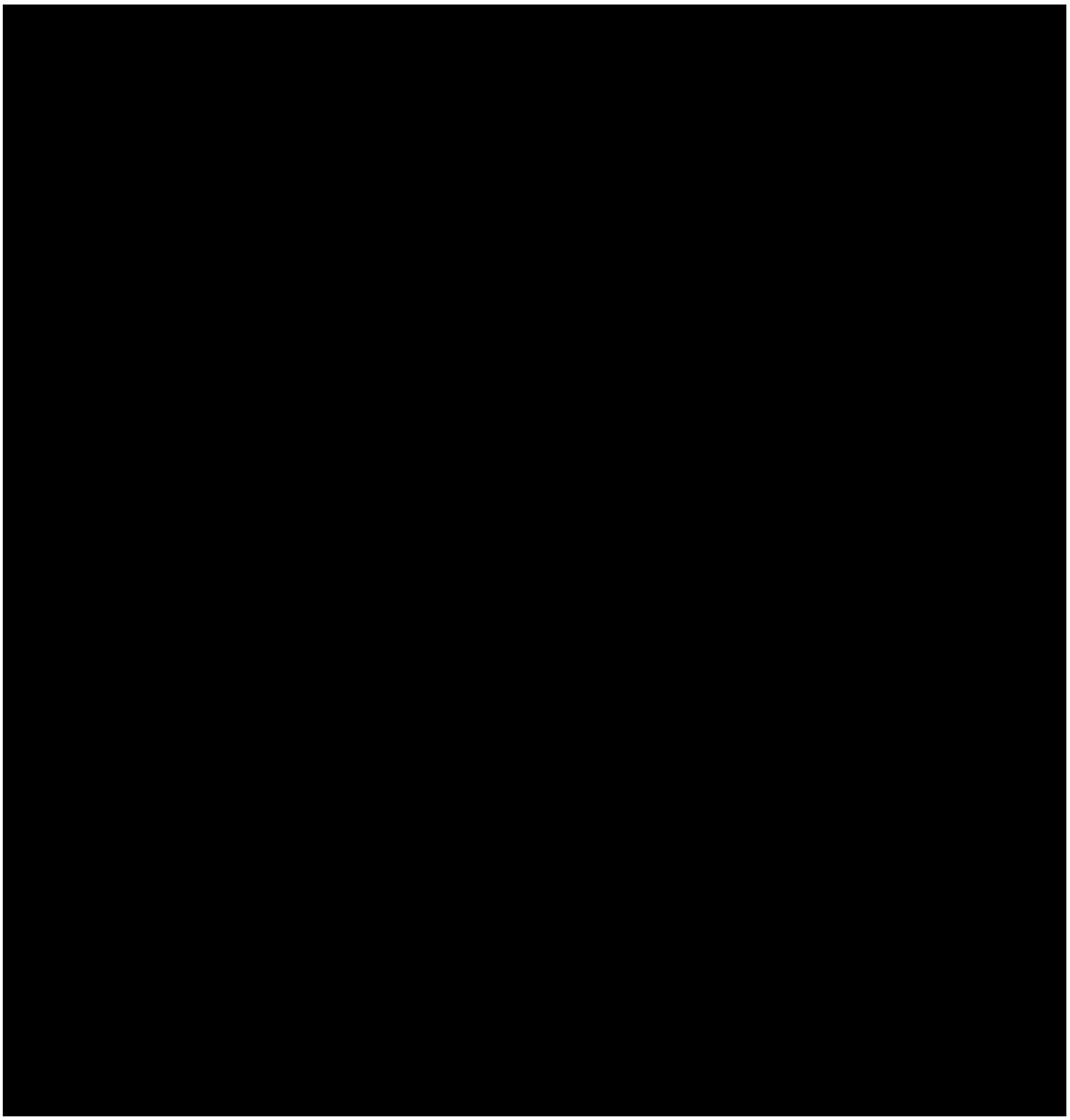


Document History

SignNow E-Signature Audit Log

All dates expressed in MM/DD/YYYY (US)

Document name:	Stuart Therapeutics Inc ST100-001 SAP draft v1.0 25-OCT-2021 clean
Document created:	10/26/2021 14:28:35
Document pages:	48
Document ID:	2fce7f547f0b437bad5cd8831715c2c12a6b22a2
Document Sent:	10/26/2021 14:31:54 UTC
Document Status:	Signed
	10/29/2021 17:36:43UTC

Table of Contents

List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
BID	*Bis in die* (Twice Daily)
CAE®	Controlled Adverse Environment
CFB	Change from Baseline
CFV2-Post	Change from Visit 2 (Day 1) Post-CAE®
CI	Confidence Interval
CRO	Contract Research Organization
CS	Clinically Significant
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OD	*Oculus dexter* (Right Eye)
OS	*Oculus sinister* (Left Eye)
PDF	Portable Document Format
PMM	Pattern Mixture Model
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SE	Standard Error

SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TMF	Trial Master File
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 amendment 1 dated 21-MAY-2021.

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, the most recent ICH E9 (R1) Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in 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 objective of this study is to compare the safety and efficacy of two different concentrations of ST-100 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of dry eye.

3. Study Variables

3.1 Primary Endpoints

The primary efficacy endpoints are the following:

- Sign: Total corneal fluorescein staining score on the Ora Calibra® scale, measured by [redacted]
- Symptom: Ocular discomfort score on the Ora Calibra® Ocular Discomfort Scale, measured by [redacted]

3.2 Secondary Endpoints

The secondary efficacy endpoints include the following:

- Fluorescein staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®): regions: [redacted]
- Lissamine green staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®): regions: [redacted]

[redacted]

- Tear film break-up time (TFBUT) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®)
- Conjunctival Redness at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®)
- Drop comfort assessment after randomization at Visit 2 and Visit 6
- Ocular Surface Disease Index (OSDI©) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®)
- Overall Ocular Discomfort and Four-symptom Questionnaire at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®)
- Ocular discomfort during CAE® at Visits 5, 6, and 7
- Daily diary
- Visual Analog Scale – Burning/Stinging, Itching, Foreign Body Sensation, Blurred Vision, Eye Dryness, Photophobia, and Pain at Visits 3, 4, 5, 6, and 7 (Pre-CAE®)
- Unanesthetized Schirmer's Test at Visit 7 (Pre-CAE®)
- Ocular Discomfort Scale outside of the CAE® at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®)

3.3 Safety Variables

The safety variables include the following:

- Best-corrected visual acuity (BCVA)
- Slit-lamp evaluation
- Adverse event (AE) query
- Intraocular pressure (IOP)
- Undilated fundoscopy

3.4 Statistical Hypotheses

The primary endpoints will be tested for [redacted] The statistical hypotheses are stated in terms of [redacted]

[redacted]

[redacted]

3.5 Estimands

The primary comparisons in this trial will be between ST-100 Ophthalmic Solution (high dose or low dose) versus placebo at Day 29 in the Intent-to-Treat (ITT) population with multiple imputation using the following primary estimand:

Estimand 1:

- Population: [redacted]
- Endpoint:
  - [redacted]
  - [redacted]
- Intercurrent event:
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

- Population-level summary:

[redacted]

4. Study Design and Procedures

4.1 General Study Design

Study visits will be referred to in all tables and listings as the visit number and 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. Study Visit Windows

Scheduled Visit	Planned Study Day	Visit Window
Visit 1	Day -7	± 1 day
Visit 2	Day 1	N/A
Visit 3	Day 2	± 2 hours
Visit 4	Day 4	± 2 hours
Visit 5	Day 8	± 1 day
Visit 6	Day 15	± 1 day
Visit 7	Day 29	± 2 days

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided in Appendix 1.

5. Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Before the initiation of study run-in at Visit 1 (Day -7), each subject who provides written informed consent will be assigned a screening number. All screening numbers will be assigned in strict numerical sequence at a site and no numbers will skipped or omitted. Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 (Day -7) 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.

Subjects will be randomized to one of the following treatment arms at Visit 2 (Day 1):

- Low dose ST-100 Ophthalmic Solution: [redacted]
- High dose ST-100 Ophthalmic Solution: [redacted]
- Placebo Ophthalmic Solution (Vehicle): [redacted]

Approximately [redacted] subjects will be randomly assigned to one of the three groups (1:1:1) to receive either ST-100 Ophthalmic Solution or placebo solution as topical ophthalmic drops administered bilaterally BID for 4 weeks. Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment. 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). Subjects, Sponsor, CRO, and site personnel will be masked to treatment assignment.

5.2 Masking and Unmasking

All subjects, investigators, and study personnel involved with the conduct of the study will be masked with regard to treatment assignments. When medically necessary, the investigator may need to determine what treatment group has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora and/or the study sponsor should be notified before unmasking study drug. 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 investigational product (IP), if possible. Ora will ask the site to complete and send them the Unmasking Request Form. Ora will notify the Sponsor 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 Trial Master File (TMF). 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. Unmasked subjects will be followed for safety monitoring until resolution of the AE or study completion, whichever occurs last.

6. Sample Size and Power Considerations

This study is expected to enroll [redacted] subjects in each group, for a total of [redacted] randomized subjects. Approximately [redacted] subjects will be screened. Assuming a 10% drop out rate, [redacted] subjects per group are expected to complete the study.

7. Data Preparation

7.1 Input Data

Study data will primarily be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using iMedNet v1.211.1.

When all prerequisites for database lock have been met, the database will be locked. Following database lock, approval will be obtained from the Sponsor to unmask the study. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified and status defined (major/minor deviations) prior to database lock.
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.2 Output Data

Data from electronic data capture (EDC) and external data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM version 1.7 model and will be implemented using the SDTM Implementation Guide version 3.3, and the most recent version of SDTM Controlled Terminology at the start of the study. ADaM data will follow the ADaM version 2.1 model and will be implemented using the ADaM

Implementation Guide version 1.2. Both SDTM and ADaM will be validated using Pinnacle 21 version 3.1.2. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

8. Analysis Populations

8.1 Intent-to-Treat

The intent-to-treat (ITT) population includes [redacted]

8.2 Per Protocol

The per protocol (PP) population includes [redacted]

8.3 Safety

The safety population includes [redacted]

9. General Statistical Considerations

9.1 Unit of Analysis

Safety endpoints will be analyzed for both eyes. For efficacy endpoints, the unit of analysis will be the study eye, or the "worst eye," as defined by the following:

Study (Worst) Eye: [redacted]

9.2 Missing or Inconclusive Data Handling

Imputation of missing data will be executed for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.
- If the ongoing flag is missing or “Yes” then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is “No” then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc).

Missing data for the primary efficacy endpoints will be imputed using multiple imputation on the ITT population as specified in Estimand 1 for primary analyses.

Sensitivity analyses of the primary efficacy analyses will include the following in order to provide a robust understanding of the impact of missing and spurious data:

9.3 Definition of Baseline

Baseline measures are defined as [redacted]

9.4 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.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians 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 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 minus baseline.

[redacted]

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit. Listings will be sorted by treatment group, subject number, visit/time point, and parameter as applicable.

9.5 Adjustments for Multiplicity

[redacted]

[redacted]

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were included in the following analysis populations: [redacted] Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by [redacted]

The total number of screened subjects with the number and percentage of screen failure subjects.

The reasons for premature study discontinuation will be summarized by treatment group for all discontinued subjects. Percentages will be calculated using discontinued subjects as the denominator. The reasons for study discontinuation that will be summarized include: AE, protocol violation, administrative reasons, sponsor termination of study, subject choice, lost to follow-up, lack of efficacy, and other. The subset of 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. The listing will indicate COVID-19 relatedness with a reason for COVID-19 relatedness.

[redacted]

[redacted]

For all screen failures, the reasons for screen failure will be displayed with the percentages calculated using total number of screen failures as the denominator.

In addition, subject listings will be provided that include informed consent date, screen failure reason, and exclusions from analysis populations. Details of the study randomization, including randomization date and time, randomized treatment, and actual treatment, will also be included within a subject listing. A listing summarizing all COVID-19-related discontinuations and protocol deviations will be generated as well.

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

The demographic variables collected in this study include age, sex, childbearing potential for female subjects, race, ethnicity, and iris color. Subjects who record more than one race will be grouped into a single category denoted as Multiple. Iris color will be summarized at the eye level (OD and OS). Demographic variables will be summarized for the ITT and 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.

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

11.2 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment group using [redacted]

[redacted]

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 24.0.

Ocular and non-ocular medical history will be summarized separately [redacted]

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

12.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global (B3, March 2021) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred name. If the ATC 4 classification is not provided, then 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 (e.g., multivitamins), then the drug name will be summarized as the preferred name. Any uncoded terms will be summarized under the ATC classification and preferred name of “Uncoded.”

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of randomized study drug administration and continuing for any period of time following the first administration of randomized study drug or (2) at any time following the first administration of randomized study drug. Prior medications are defined as those listed as having been prior to initiation of randomized study drug administration but not taken for any instance following the first administration of randomized study drug.

[redacted]

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

12.3 Concomitant Procedures

Concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 24.0.

[redacted]

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

13. Dosing Compliance and Treatment Exposure

13.1 Dosing Compliance

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

[redacted]

The number of actual doses received will be calculated from the number of used ampules from the study drug accountability eCRF. The number of expected doses that will be used for calculating compliance will be calculated as:

[redacted]

for all subjects with exception of subjects that are lost to follow-up. The number of expected doses for subjects that are lost to follow-up will be calculated as:

[redacted]

The number of expected doses for subjects who discontinue on visit 2 will be 2 doses.

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 Safety population. The compliance category defined above will be summarized with discrete summary statistics.

A subject listing of dosing compliance will also be produced. In addition, the following listings will be produced for all randomized subjects:

- run-in and study drug assignment, dispensation, replacement, and study drug instillation;
- study drug accountability;

13.2 Treatment Exposure

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

[redacted]

Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

[redacted]

The extent of treatment exposure for subjects who discontinue on Visit 2 (Day 1) will be 1 day.

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

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy endpoints are the following:

[redacted]

14.1.1 Change from Baseline of Total Corneal Fluorescein Staining (Ora Calibra® Scale) in the Study Eye at Visit 7 (Day 29) Pre-CAE®

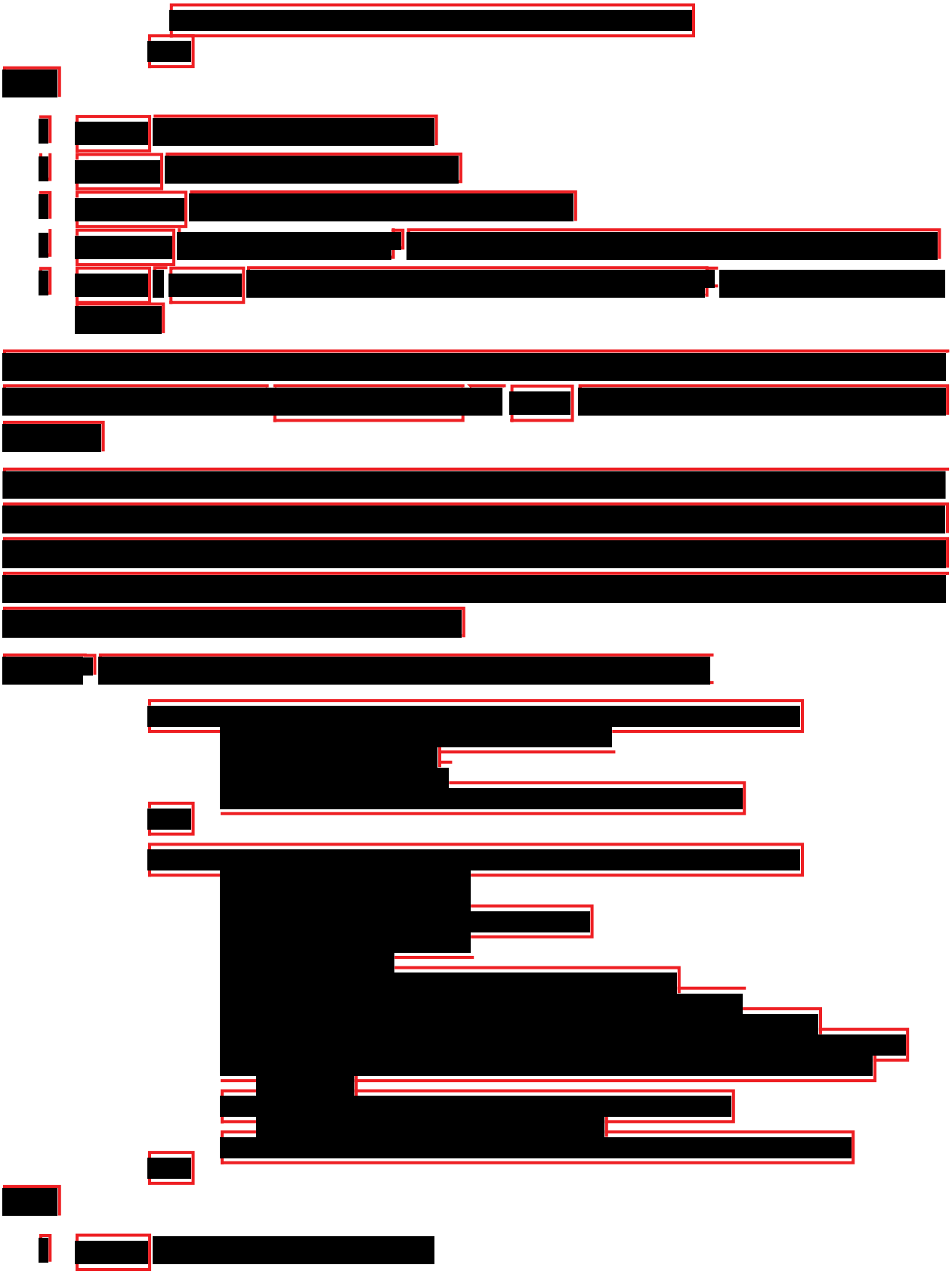
[redacted]

14.1.1.1 Primary Analysis Methods

[redacted]

14.1.1.2 Multiple Imputation Methodology

[redacted]



[redacted]

14.1.1.4 FIGURES

[redacted]

14.1.2 CHANGE FROM BASELINE OF OCULAR DISCOMFORT (ORA CALIBRA® SCALE) IN THE STUDY EYE AT VISIT 7 (DAY 29) PRE-CAE®

[redacted]

14.1.2.1 PRIMARY ANALYSIS METHODS

[redacted]

14.1.2.2 MULTIPLE IMPUTATION METHODOLOGY

[redacted]

[redacted]

14.1.2.3 ADDITIONAL SENSITIVITY ANALYSES

Additional sensitivity analyses will be conducted as described in Section 14.1.1.3.

14.1.2.4 FIGURES

[redacted]

14.2 Secondary Analyses

The secondary efficacy variables include the following:

- Fluorescein staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Change from Pre-CAE® to Post-CAE®): regions: [redacted]
- Lissamine green staining (Ora Calibra® scale) at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Pre- to Post-CAE®): regions: [redacted]
- TFBUT at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Change from Pre-CAE® to Post-CAE®)
- Conjunctival Redness at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Change from Pre-CAE® to Post-CAE®)
- Drop comfort assessment after randomization at Visit 2 and Visit 6
- OSDI© at Visits 3, 4, 5, 6, and 7 (Pre-CAE®)
- Four symptom questionnaire at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Change from Pre-CAE® to Post-CAE®)
- Ocular discomfort during CAE® at Visits 5, 6, and 7
- Daily diary
- Visual Analog Scale – Burning/Stinging, Itching, Foreign Body Sensation, Blurred Vision, Eye Dryness, Photophobia, and Pain at Visits 3, 4, 5, 6, and 7 (Pre-CAE®)

- Unanesthetized Schirmer's Test at Visit 7 (Pre-CAE®)
- Ocular Discomfort Scale outside of the CAE® at Visits 3, 4, 5, 6, and 7 (Pre-CAE®, Post-CAE®, and Change from Pre-CAE® to Post-CAE®)

14.2.1 Analysis of Secondary Endpoints

[redacted]

Subject listings will be provided for all efficacy endpoint assessments for randomized subjects only.

14.2.2 Corneal and Conjunctival Fluorescein staining (Ora Calibra® scale)

[redacted]

14.2.3 Corneal and Conjunctival Lissamine Green staining (Ora Calibra® scale)

[redacted]

14.2.4 Tear Film Break-Up Time

[redacted]

[redacted]

14.2.5 Conjunctival Redness (ORA Calibra Scale)

[redacted]

14.2.6 Drop Comfort Assessment

[redacted]

14.2.7 Ocular Surface Disease Index

[redacted]

[redacted]

[redacted]

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

[redacted]

14.2.9 Ocular Discomfort Scale (ORA Calibra® Scale)

[redacted]

[redacted]

14.2.9.1 Ocular Discomfort Outside of the CAE®

Analyses will be conducted as described in Section 14.2.1.

[redacted]

14.2.9.2 Ocular Discomfort During the CAE®

[redacted]

14.2.10 Visual Analog Scale

[redacted]

14.2.11 Unanesthetized Schirmer's Test

[redacted]

Analyses will be conducted as described in Section 14.2.1.

15. Summary of Efficacy Analyses

[redacted]

16. Safety Analyses

All safety analyses will be conducted using the safety population.

16.1 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. 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 24.0.

Treatment-emergent adverse events (TEAE) are defined as any event that occurs or worsens on or after the first dose of randomized study drug..

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 IP 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 IP 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 uncertain to the investigational product. Likely to be related to factors other than investigational product but cannot be ruled out with certainty.
- *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.

TEAEs that are recorded as definitely related, probably related, and possibly related are considered as treatment-related TEAEs.

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- Unexpected: An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.
- Expected: An AE that is listed in the IB at the specificity and severity that has been observed.
- Not applicable: An AE unrelated to the IP.

All AEs that are mentioned in the IB as occurring with a class of products or as anticipated from the pharmacological/mechanical (or other) properties of the product but are not specifically mentioned as occurring with the particular product under investigation are to be considered unexpected

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one AE, ocular AE, and non-ocular AE by treatment group and over all subjects. This summary will also include the number of events and the number and percentage of subjects who experienced at least one TEAE, as well as breakdowns of TEAEs further categorized as ocular or non-ocular, TEAEs by severity, TEAEs by relationship to study drug, TEAEs causing premature treatment discontinuation, and SAEs. TE-SAEs will also be categorized as ocular or non-ocular, TE-SAEs by severity, TE-SAEs by relationship to study drug, TE-SAEs causing premature treatment discontinuation, and TE-SAEs leading to death.

Summaries will be provided for the following categories of AEs:

- Ocular and non-ocular TEAEs by SOC and PT
- Ocular and non-ocular TEAEs by SOC, PT, and maximal severity
- Ocular and non-ocular treatment-related TEAEs by SOC and PT
- Ocular and non-ocular TE-SAEs by SOC and PT
- Ocular and non-ocular TEAEs by SOC, PT and study day of onset (Day 8 or prior, After Day 8 to Day 15, and After Day 15 to Day 29).

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 summaries, SOCs and PTs within SOCs will be listed in order of descending frequency for all subjects.

All AEs for screened subjects, ocular AEs, non-ocular AEs, and SAEs for randomized subjects will be presented in subject listings.

16.2 Best-Corrected Visual Acuity (Early Treatment Diabetic Retinopathy Study)

[redacted]

16.3 Slit-Lamp Biomicroscopy Examination

[redacted]

16.4 Intraocular Pressure

[redacted]

16.5 Undilated Fundoscopy Examination

[redacted]

16.6 Urine Pregnancy Test

[redacted]

17. Interim Analyses

No interim analyses are planned.

18. Changes from Protocol-Stated Analyses

CFB-V2 Post as defined in section 9.3 of this SAP will be analyzed at Visit 3 (Day 2), Visit 4 (Day 4),Visit 5 (Day 8) Pre-CAE®, Visit 6 (Day 15) Pre-CAE®, and Visit 7 (Day 29) Pre-CAE®.

19. References

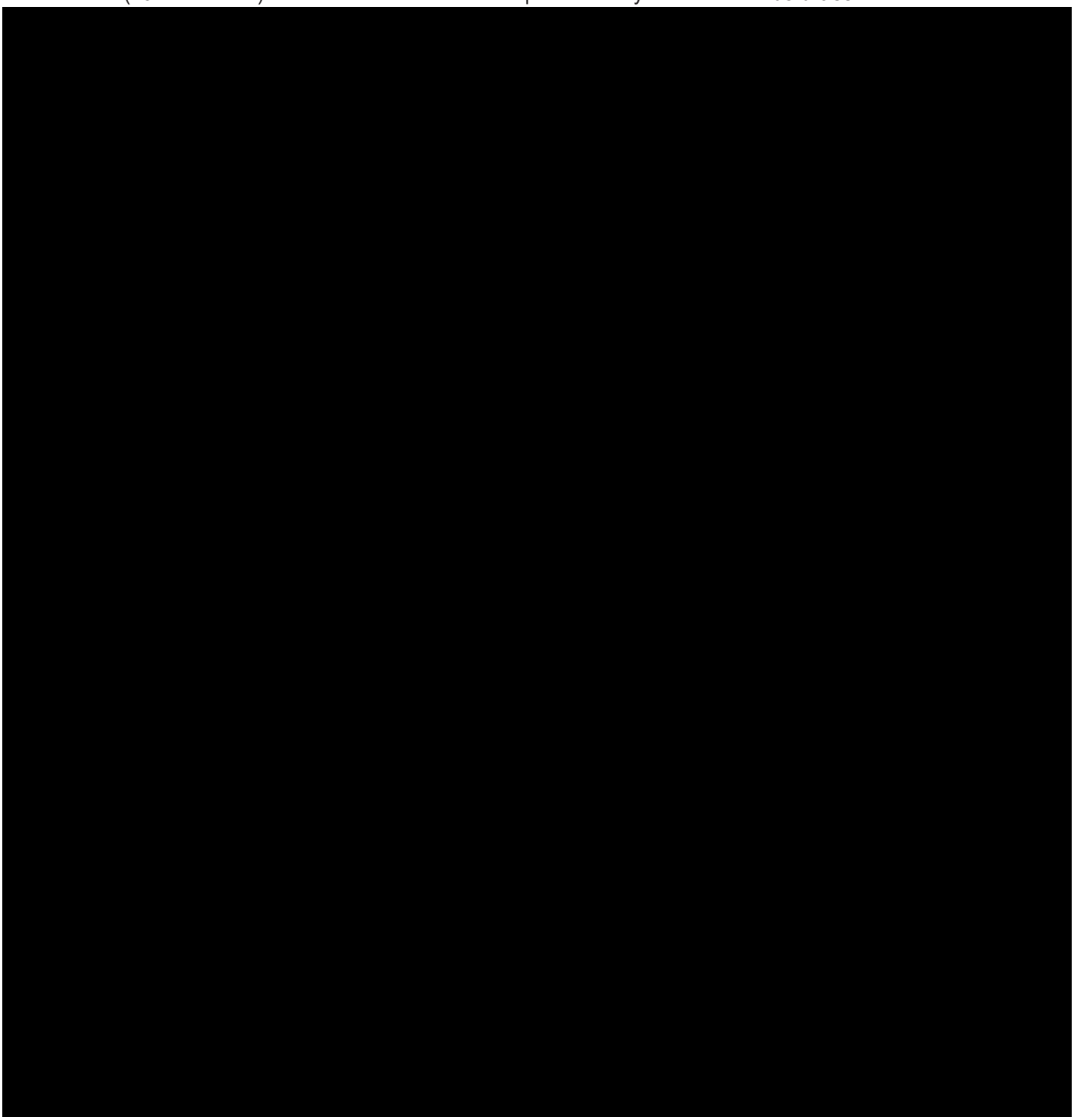
There are no applicable references for this SAP.

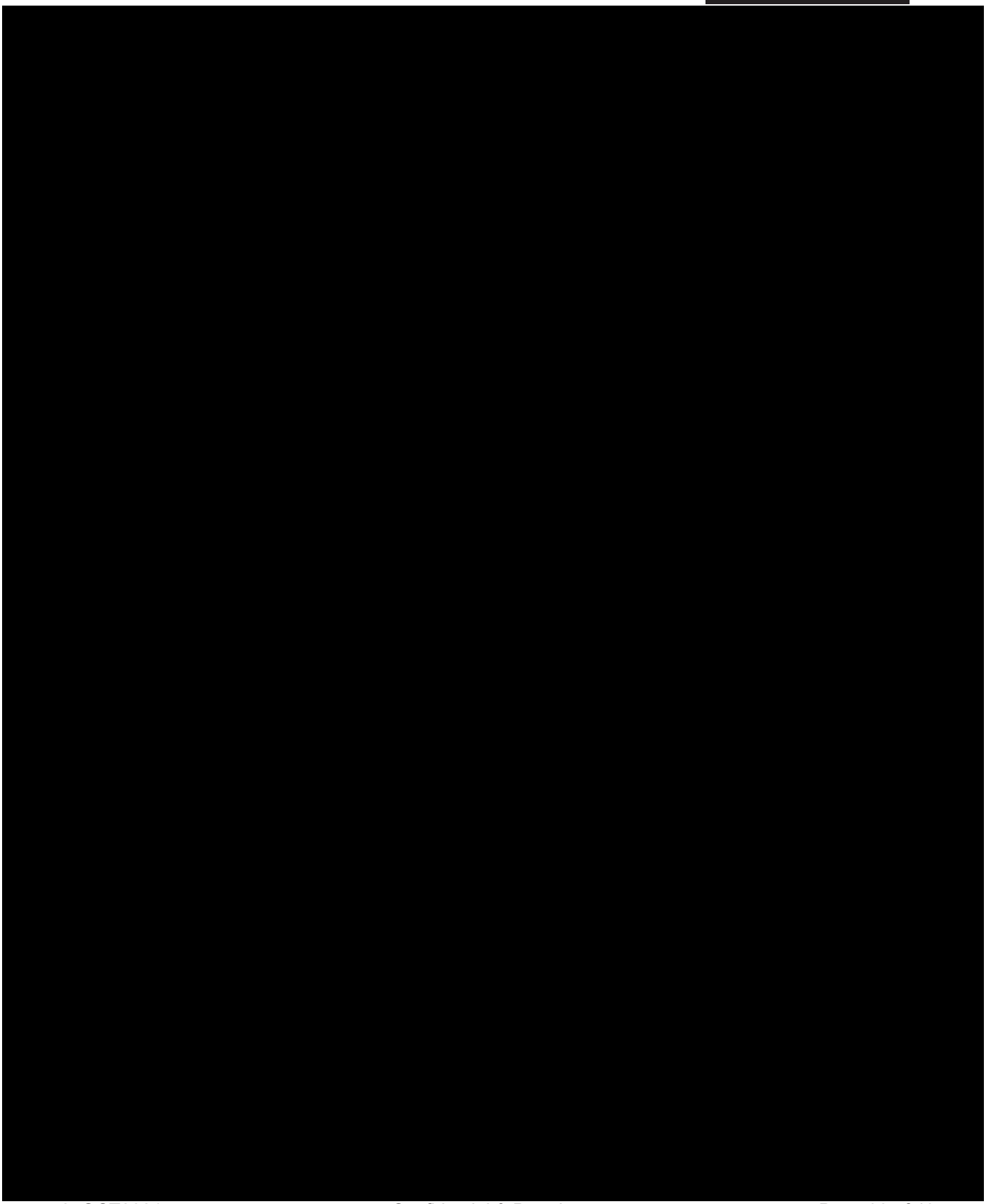
20. Revision History

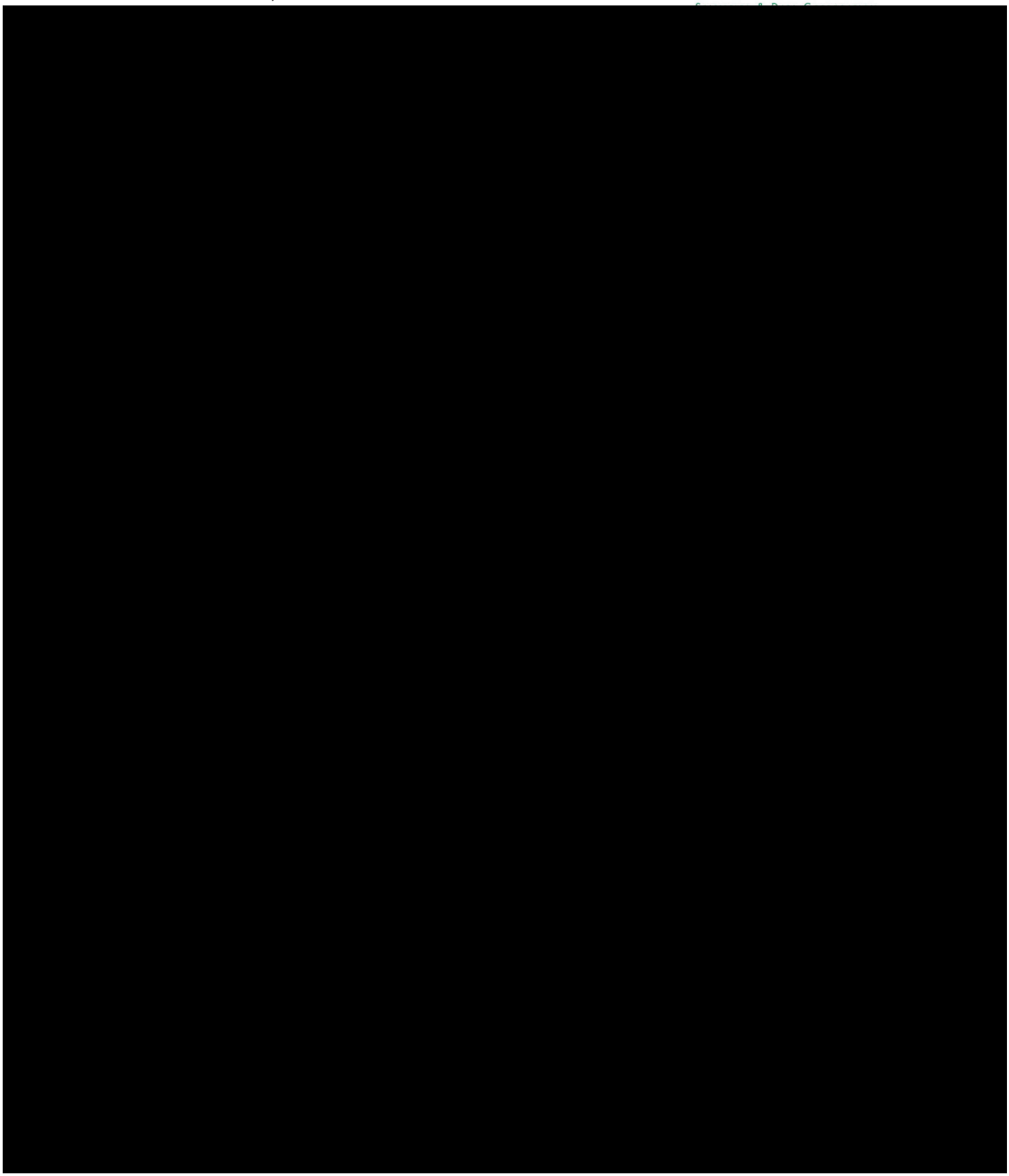
Documentation of revision to the SAP will commence after approval of the final version 1.0.

21. Tables

Tables (10 tables total) that will be included in the topline delivery are shown in **boldface** font.







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22. Listings

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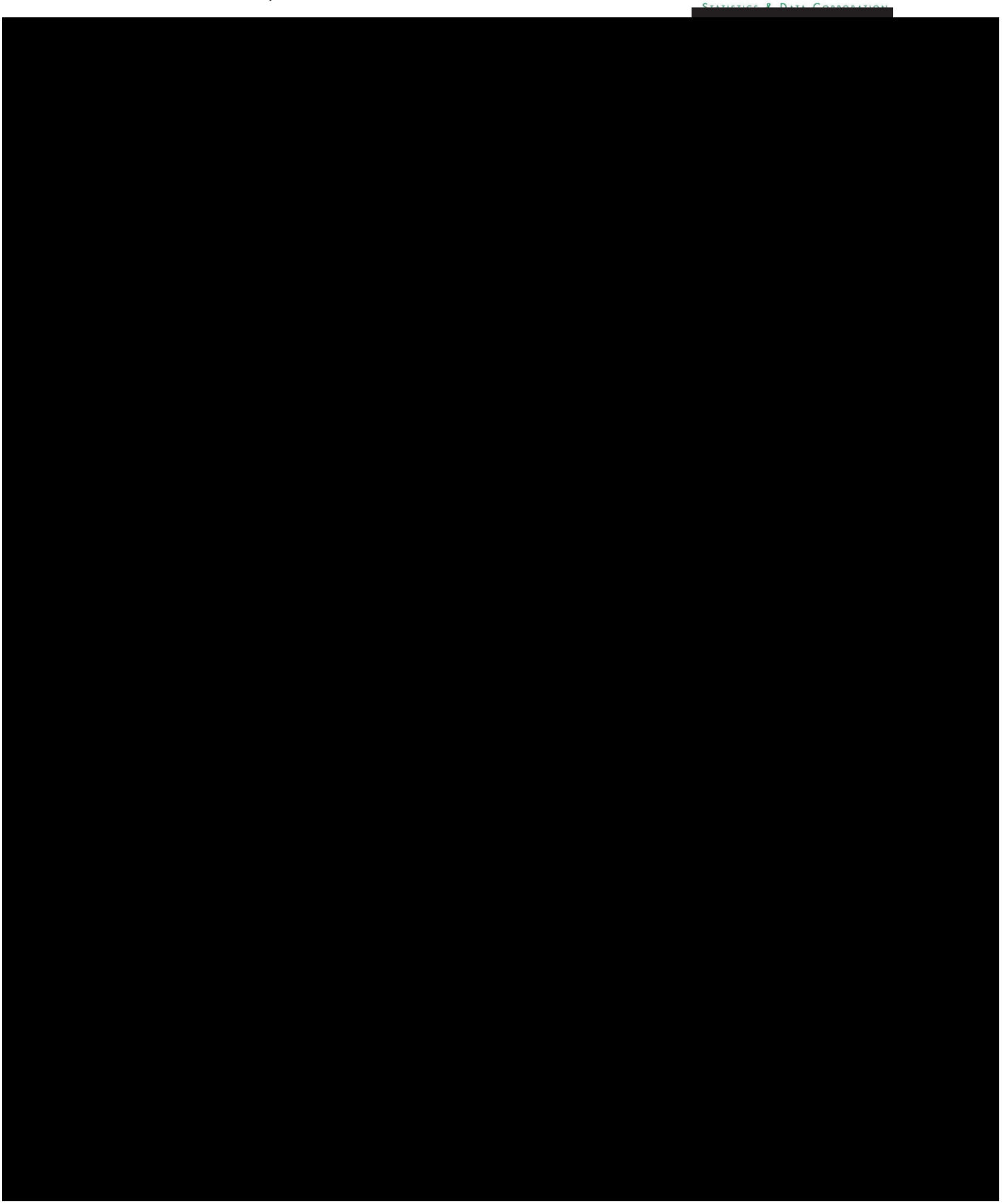

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23. Figures

[redacted]

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24. Appendices

24.1 Appendix 1: Schedule of Visits and Measurements

[redacted]