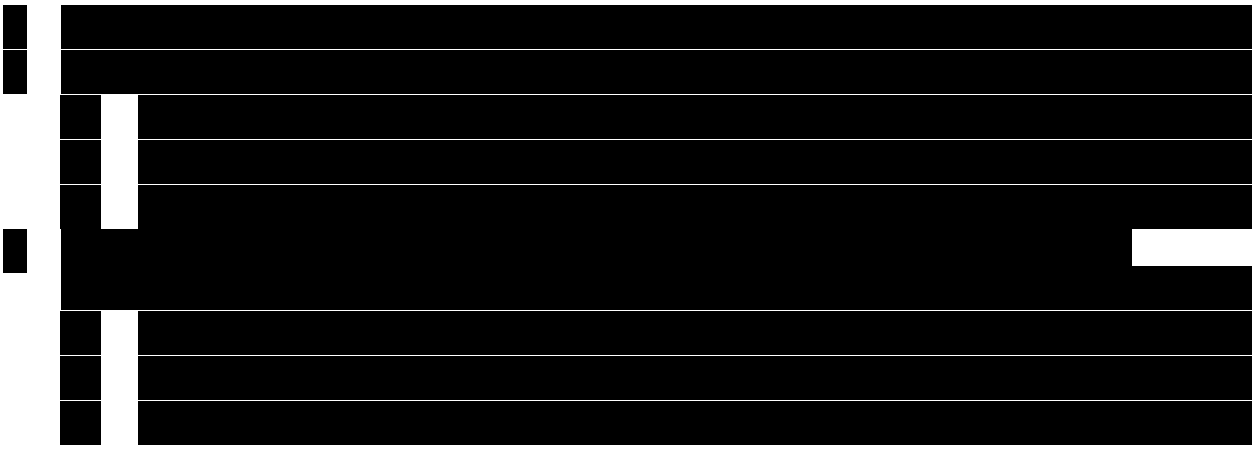
STATISTICAL ANALYSIS PLAN

Protocol Number:	1820205
Title:	A Phase 2a, Multicenter, Open-Label, Dose-Escalation Study to Evaluate the Efficacy, Safety, and Duration of Benefit of Increasing Doses of DaxibotulinumtoxinA for Injection (DAXI for injection) in the Treatment of Moderate or Severe Lateral Canthal Lines
Study Phase:	2a
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA 94560
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Date:	01 Jun 2020
SAP Version Number:	Version 2.0
Protocol Version:	Amendment 2, 14 Aug 2019

[redacted]

TABLE OF CONTENTS



LIST OF TABLES

[redacted]

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
CI	Confidence interval
DAXI	DaxibotulinumtoxinA
FASE	Facial Age Self Evaluation
DRC	Data Review Committee
FASE	Facial Age Self Evaluation
GAIS	Global Aesthetic Improvement Scale
GL	Glabellar lines
IGA-LCWS	Investigator Global Assessment Lateral Canthal Wrinkle Severity
LCL	Lateral canthal lines
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PLCWS	Patient Forehead Wrinkle Severity
PI	Principal Investigator
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
UPT	Urine pregnancy test
WOCBP	Women of childbearing potential

1. INTRODUCTION

The efficacy and safety of onabotulinumtoxinA for the treatment of lateral canthal lines (LCL) has been evaluated in a large-scale clinical development program consisting of 3 phase 3 studies (Carruthers, 2015b). Study 1 evaluated onabotulinumtoxinA for the treatment of LCL alone in a total of 445 subjects. Study 2 was a 7-month, double-blind, randomized, placebo-controlled, parallel-group study with 2 treatment cycles of onabotulinumtoxinA or placebo in a total of 917 subjects. Study 3 was a 5-month, double-blind, randomized, parallel-group, placebo-controlled extension study of the subjects who completed Study 2.

The Sponsor, Revance Therapeutics, Inc. (Revance), has conducted 5 studies to examine the safety and [redacted]

[redacted]

This study will complement the available data from the dose-ranging GL and forehead lines study to provide a better understanding of the safety and efficacy of DAXI for injection in the treatment of the upper face rhytides.

This statistical analysis plan (SAP) describes the objectives of the study and the safety and efficacy assessments that are collected. The safety endpoints and the efficacy endpoints are defined, and the statistical methods used to analyze them are presented. Table shells for the planned end-of-text tables, figures, and listings are included in a separate document, but the titles are specified following the text of the SAP.

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

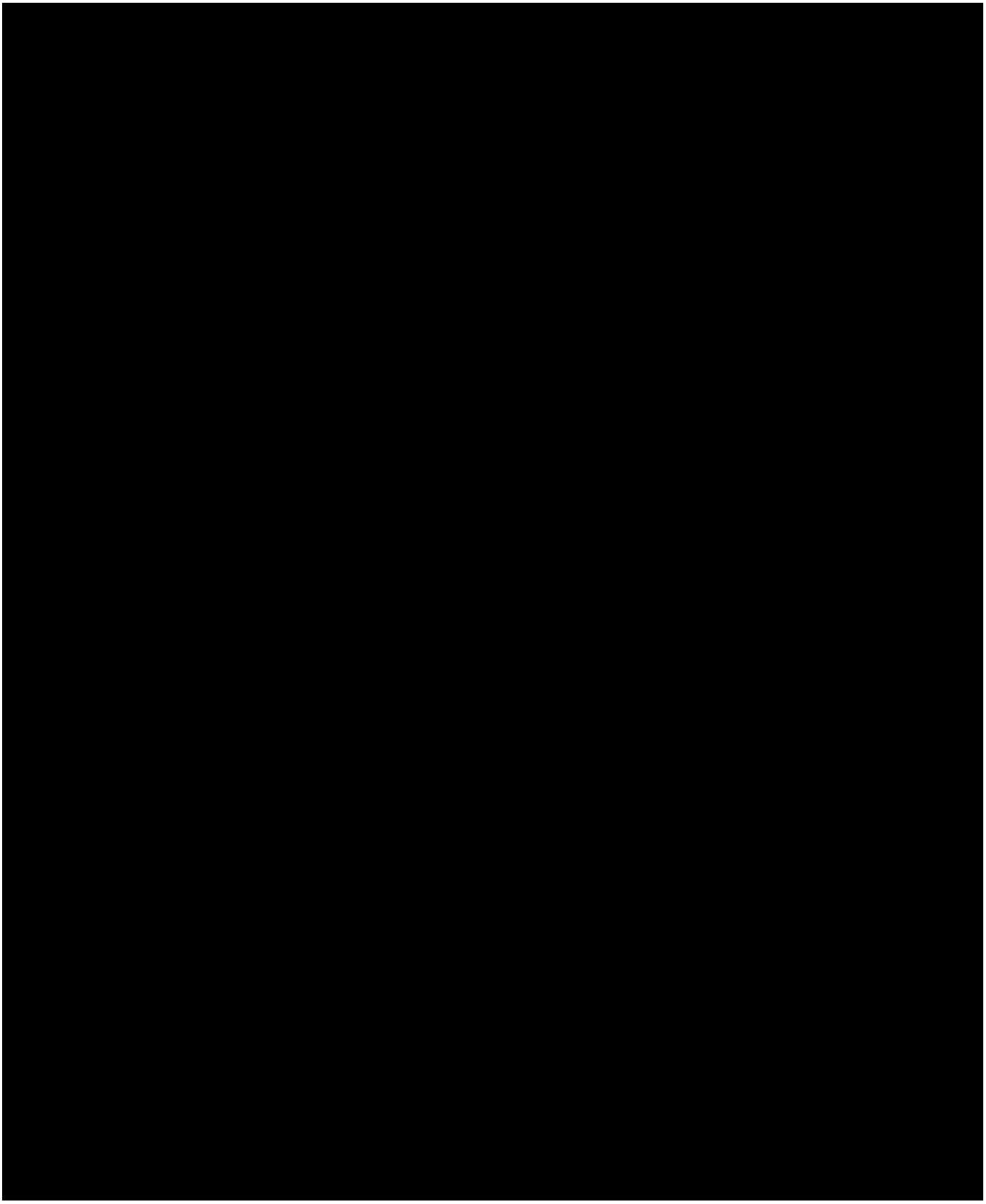
The primary study objective is to evaluate the efficacy and safety of DAXI for injection in the treatment of dynamic lateral canthal lines (LCL).

[redacted]

2.2 Trial Endpoints

2.2.1 Efficacy Endpoints

The primary efficacy endpoint is the proportion of subjects achieving a score of 0 or 1 (none or mild) in LCL severity at maximum smile at Week 4 after LCL treatment on the Investigator Global Assessment of Lateral Canthal Wrinkle Severity (IGA-LCWS) scale.



2.2.2 Safety Endpoints

The primary safety endpoint is the incidence, severity, and relationship to study drug of TEAEs and SAEs during the overall study duration.

3. OVERALL STUDY DESIGN AND PLAN

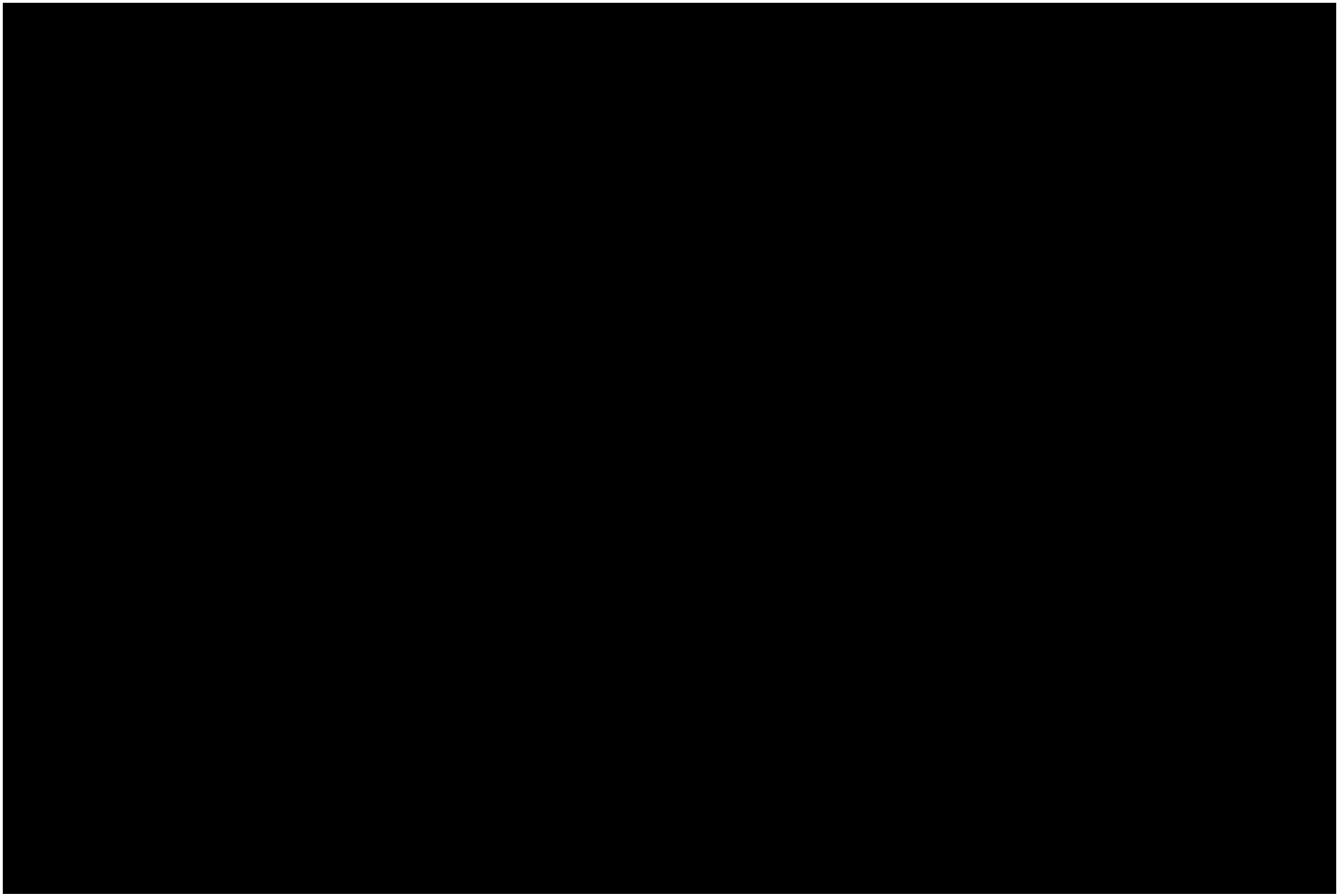
3.1 Study Design

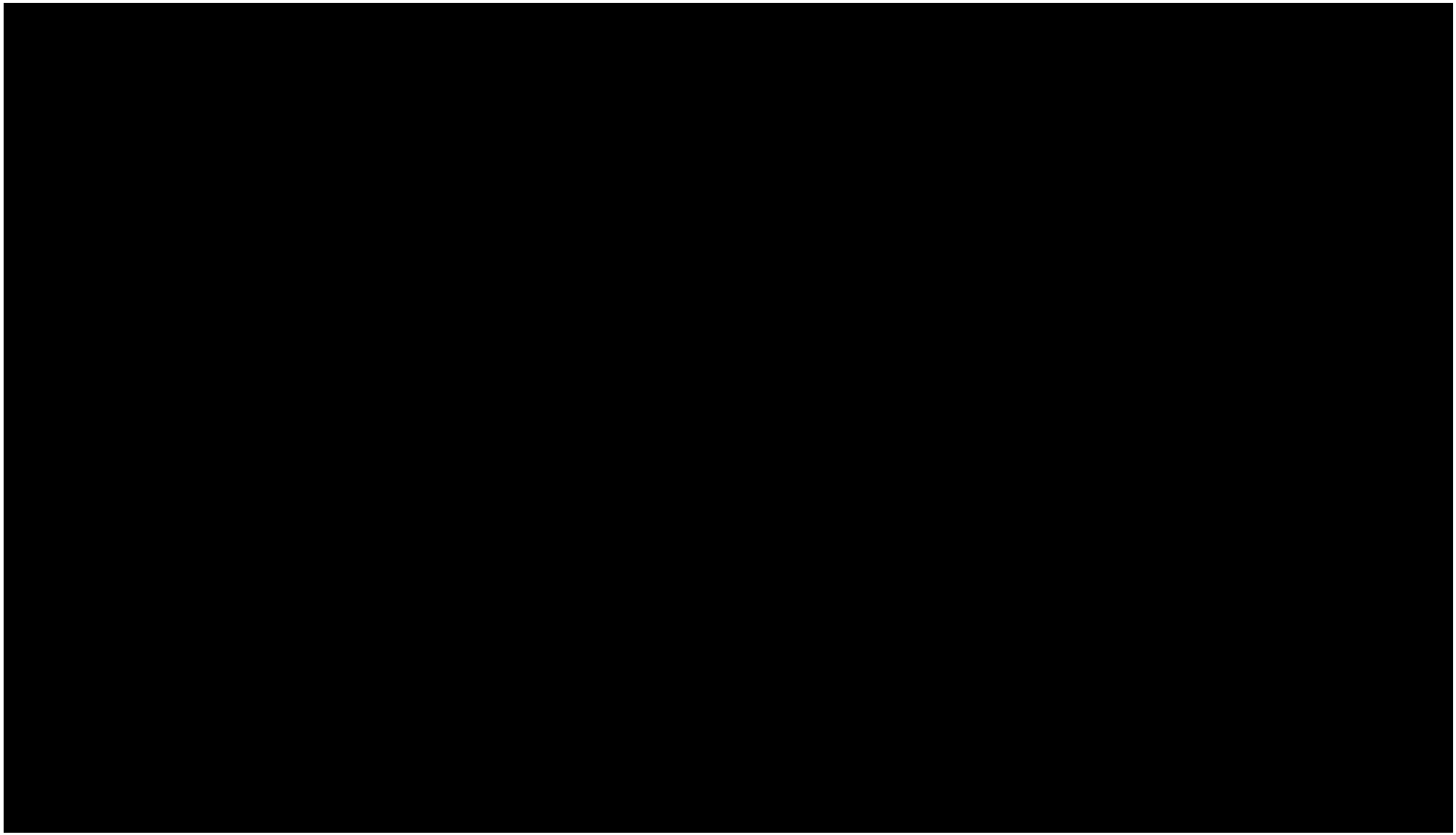
This is a phase 2a, multicenter, open-label, dose-escalation study to evaluate the safety and efficacy of DAXI for injection for the treatment of subjects with moderate to severe LCL. This study will be conducted at 4 sites in the United States.

[redacted]

Approximately 64 subjects (18-65 years of age) with moderate to severe LCL will be enrolled [redacted] The total study duration will be up to 38 weeks including up to 2 weeks for screening. Subjects will be followed for a minimum of 24 weeks and up to 36 weeks or until scores on the IGA-LCWS and PLCWS return to baseline (Day 1 Visit) or until Week 36, whichever occurs first. Subjects will then have a Final Evaluation Visit. [redacted]

A Data Review Committee (DRC) will be used to review available data and will determine whether to proceed to the subsequent cohorts. Cohorts 1 and 2 will be enrolled simultaneously and the DRC will review data 4 weeks after LCL treatment for the last subject in Cohorts 1 and 2. The DRC will convene again after the last subject in Cohort 3 reaches the Week 4 visit.





3.1.1 Determination of Sample Size

The sample size is not determined by the power of formal hypothesis tests. [redacted]

3.1.2 Treatments Administered

This is an open-label, non-randomized study for the treatment of moderate or severe LCL. Subjects will be sequentially enrolled by cohort. [redacted]

3.2 Efficacy and Safety Assessments

The primary effectiveness assessments will include investigator assessment of LCL severity and improvement, as well as subject assessment of severity and improvement on the IGA-LCWS and PLCWS, respectively.

3.2.1 Lateral Canthal Wrinkle Severity – Patient and Investigator Global Assessment

Lateral canthal wrinkle severity is assessed by both the subject (PLCWS) and the investigator (IGA-LCWS) using the same 4-point rating scale, where scores range from 0 = none to 3 = severe.

3.2.2 Global Aesthetic Improvement Scale

The Investigator and subject will assess the visual appearance (at maximum smile) of the improvement from the baseline condition in LCL using the 7-point severity GAIS. The scale ranges from -3 = Very much worse to 3 = Very much improved, with a rating of 0 = No change.

3.2.3 Facial Age Self Evaluation

At each clinic visit, the subject will be asked to rate their perceived age using the FASE questionnaire (see Appendix 7 of the protocol).

3.2.4 FACE-Q™

At each clinic visit, the subject will be asked to complete the FACE-Q™ Appraisal of Lines: Crow's Feet Lines questionnaire (see Appendix 9 of the protocol). The questionnaire asks subjects to rate how bothered they are by their LCL using 7 questions about general appearance with a rating scale of 1 to 4 with 1 = Not Bothered and 4 = Extremely Bothered.

[redacted]

[redacted]

3.2.7 Subject Global Satisfaction with Treatment Questionnaire

At each clinic visit after treatment, the subject will be asked to complete the Subject Global Satisfaction with Treatment Questionnaire to rate their satisfaction with the treatment results using a 7-point scale. The scale ranges from 0 = Very Dissatisfied to 6 = Very Satisfied, with a rating of 3 = Neither Satisfied nor Dissatisfied.

3.3 Safety Assessments

3.3.1 Adverse Events

All adverse events (AEs) will be recorded and classified on the basis of MedDRA terminology. AE severity will be graded as mild, moderate, or severe as defined in Section 8.5.7 of the protocol. Relationship of an AE will be graded as definite, probable, possible, or unrelated. AEs with an onset on or after the date and time of trial treatment or events which were present before treatment and which worsened after treatment will be considered as treatment-emergent.

AEs with missing severity will be considered as "severe". AEs with missing relationship will be considered as "related". If the start of an AE relative to the administration of trial treatment cannot be definitively determined, it will be considered to have occurred after treatment and the event considered as treatment-emergent.

[redacted]

3.3.3 Injection Site Evaluation

Injection sites will be evaluated at screening for signs of skin inflammation or active disease and at Day 1 (pre- and post-treatment), Week 2 and Week 4 visits. The assessment will be done as a global evaluation of the 3 injection sites for LCL on each side of the face. The presence of erythema, edema, burning or stinging, itching or bruising will be captured as medical history (pre-treatment) or as an AE (post-treatment).

3.3.4 Clinical Laboratory Data

3.3.4.1 Clinical Safety Laboratory Data

As outlined in Table 3.3.4-1, non-fasting samples for hematology, chemistry, PT (screening only) and urinalysis will be collected at screening, the Week 4 Visit, and the Week 36 or Final Evaluation Visit. [redacted] Urinalysis will be evaluated at the study center.

Table 3.3.4-1: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose	Hemoglobin	Specific gravity	Prothrombin time (PT; screening only)
Total bilirubin	Hematocrit	pH	
Alanine aminotransferase	Leukocyte Count (total)	Glucose	UPT (WOCBP only)*
		Protein	
Aspartate aminotransferase	Leukocyte Count (differential)	Blood	[redacted]
		Bilirubin	
Alkaline phosphatase	Red Blood Cell Count	Ketones	
Blood urea nitrogen	Platelet Count		

WOCBP = Women of child-bearing potential

3.3.4.2 Pregnancy Test

Urine pregnancy tests (UPT) will be performed at screening, baseline (prior to treatment) and at the Week 36 or Final Evaluation Visit. A serum pregnancy test will be performed to confirm pregnancy whenever a post-treatment UPT is positive.

[redacted]

3.3.5 Vital Signs

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained at the screening, Day 1, Week 2, and Week 36 or Final Evaluation Visits, [redacted]. New abnormal findings or worsening from baseline (Day 1 prior to LCL treatment) at subsequent assessments, if judged clinically significant, should be recorded as an AE.

3.3.6 Physical Examination

A targeted physical examination, [redacted] will be conducted at screening, Day 1, Week 2 and Final Evaluation Visits. Significant physical examination findings that are present prior to investigational product administration will be reported as Medical History.

Significant physical examination findings after investigational product administration which meet the definition of an AE will be recorded as an AE.

[redacted]

3.4 Interim Analyses and Data Monitoring

3.4.1 Data Review Committee

Due to the dose-escalation nature of the study design, safety data and subject photographs/videos will be evaluated by the DRC at Week 4 following LCL treatment in Cohorts 1 and 2 (enrolled simultaneously) before a decision is made to move forward with the next and subsequent doses. The DRC will reconvene again after the last subject in Cohort 3 reaches the Week 4 Visit. Safety data will be monitored throughout the study by the DRC at regular intervals.

Dose escalation for LCL may be stopped at the discretion of the DRC as outlined in the DRC Charter. The full details for the roles and responsibilities of the DRC will be detailed in the study-specific DRC charter.

3.4.2 Interim Analysis

A formal interim analysis of the data will be performed when all subjects finish 8 weeks after receiving the LCL treatment or have withdrawn from the study earlier. This interim analysis will be a high level analysis of study conduct, efficacy and safety. The analysis will be performed by the study team in a restricted access folder. Efficacy will focus on the primary and secondary endpoints.

Individual tables, listings, and figures to be included in the interim analyses are denoted in Section 9 below with an asterisk.

4. ANALYSIS POPULATIONS AND SUMMARY GROUPS

Three analysis populations will be specified, ignoring cohort membership. These populations are: Enrolled, LCL-Evaluable, and Safety. Analyses performed will be based on the actual dose for LCL received (which is expected to be consistent with the enrollment cohort).

4.1 Enrolled Population

All subjects who receive the LCL treatment. A subject will be considered "enrolled" if they receive any investigational product including a partial dose.

4.2 LCL-Evaluable Population

All enrolled subjects who receive the LCL treatment and have any post-LCL treatment assessment of IGA-LCWS at maximum smile.

4.3 Safety Population

All enrolled subjects.

[redacted]

5. CONVENTIONS AND DERIVATIONS

5.1 Definition of Baseline

The baseline value will be the last available non-missing value prior to LCL treatment on Day 1. Assessments taken on the same day as LCL treatment will be assumed to be prior to treatment unless indicated to be obtained post-treatment.

5.2 Definition of Day 1

Day 1 of LCL treatment is defined as the day of DAXI dose for LCL treatment. All time-to-event analyses for assessments of LCL will utilize the date of LCL treatment as the start date.

5.3 Demographic and Disposition

Age in years at time of enrollment will be derived relative to the date of informed consent as (consent date – date of birth + 1)/365.25 and truncated to 0 decimal points. Age will also be categorized into two groups: <65 years and ≥65 years.

[redacted]

5.4 Prior and Concomitant Medications

Prior therapies and medications are those which began and were stopped before receipt of study medication. Concomitant therapies and medications are those which were ongoing at the receipt of study medication and those which were taken during the study (i.e., between the date of first dose and the last study visit).

[redacted]

5.7 FACE-Q™

The FACE-Q™ assessments will be scored and converted to a transformed score which ranges from 0 to 100 according to scoring rules for the assessment. Section 8.1 for scoring of the FACE-Q™ Satisfaction Appraisal of Lines: Crow's Feet Lines.

5.8 Adverse Events

Treatment-emergent AEs are those AEs with an onset on or after the date and time of trial treatment or events which were present before treatment and which worsened after treatment.

AEs with missing severity will be summarized as "severe". AEs with missing relationship will be summarized as "related".

6. STATISTICAL METHODS

All statistical programming will be performed using statistical analysis system (SAS) version 9.4 or higher.

[redacted]

6.1 Subject Disposition

The number and percentage of subjects who have signed informed consent, enrolled, received treatment, and completed visits will be tabulated by summary cohort and overall; and, included in a listing. Reasons for not completing the study will also be tabulated by summary cohort and overall using numbers and percentages; this data will also be included in a listing. For those subjects who are considered to have failed screening, the reason(s) for failure will be provided in a listing.

The number and percentage of subjects included and excluded from the analysis populations will be tabulated overall and for each summary cohort. Reason(s) for exclusion from each population will be summarized and listed.

A summary of the duration of the subject participation in the study will be produced, including the n, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum duration in weeks, as well as the number and percentage of subjects in the duration categories.

Major protocol deviations will be listed and summarized by summary group.

6.2 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics by summary cohort and overall.

Demographic data include age, age category, sex, ethnicity, and race. Baseline characteristics include prior Botulinum toxin Type A, time since last prior Botulinum toxin Type A injection, and Fitzpatrick skin type, as well as the baseline values of the efficacy assessments, PLCWS and IGA-LCWS. Summaries will be produced for the Enrolled population. If the LCL Evaluable or Safety population differs from the Enrolled population, then the summaries will be produced for the population(s) which differ from the Enrolled population.

6.3 Medical History

Medical history will be classified on the basis of MedDRA terminology, using the latest terminology at the time of database finalization. Medical history will be summarized for the Safety population by summary cohort and overall, by system organ class, and by preferred term; and, will be listed.

6.4 Prior and Concomitant Medications

Prior therapies/medications and concomitant therapies/medications will be coded using the World Health Organization (WHO) drug dictionary and summarized by Anatomical Therapeutic Chemical (ATC) second level term and Preferred Name for the Safety population. Prior and concomitant medications will be summarized separately.

6.5 Efficacy Analyses

Descriptive statistics will be provided for all efficacy variables at all visits by cohort. A 95% exact CI will be provided for proportions. All analyses displaying proportions will use population counts as denominators at all visits regardless of the number of actual observations recorded. Differences between cohorts will not be presented except where specifically identified in the shells.

6.5.1 Primary Efficacy Analysis

The proportion of subjects achieving a score of 0 or 1 (none or mild) in LCL severity at maximum smile on the IGA-LCWS at Week 4 after LCL treatment will be summarized. An exact 95% confidence interval for the individual proportions will be provided. A Cochran-Mantel-Haenszel test of association, stratified by baseline IGA-LCWS severity and study center, will be performed. In addition, an exact Cochran-Armitage test for trend, ignoring the stratification factors, will be performed. If the Cochram-Mantel-Haenszel test is significant at the 0.05 significance level, then a linear regression on response will be performed with categorical dose and site as predictors. An unstratified logistic regression analysis may still be used to explore the dose-response relationship.

Additionally, the change from baseline in LCL Severity at Week 4 on the IGA-LCWS at maximum smile will be analyzed using a general linear model with change from baseline as the dependent variable. The model will include baseline severity and study center as fixed categorical effects. The least-square means and standard errors will be presented. Additionally, the differences between dose groups will be presented with corresponding 95% confidence intervals.

[redacted]

6.5.3.2 Time to Return to, or Time to Loss of, a Given State

The time to return to a given state, or time to loss of a given criterion, will be summarized with point estimates of median duration and 2-sided, 95% CIs, using the log-log transformation by summary cohort. Estimates of survival rates and the 2-sided, 95% CI, using the log-log transformation will also be provided. Kaplan-Meier survival curves will be plotted such that each summary group is a separate line in the same plot. This approach corresponds to the following exploratory endpoints:

- Median time to return to baseline or worse in LCL severity on both the IGA-LCWS and PLCWS at maximum smile

6.5.3.3 Proportions in a Given Category

Changes from baseline in LCL severity will be categorically summarized using number and percentages by summary cohort by visit. Separate summaries will be performed for the IGA-LCWS and the PLCWS.

Subject diary of PLCWS to assess the onset of response (decrease from baseline of at least 1 point) will be summarized categorically.

Responses to the Subject Global Satisfaction with Treatment and FASE questionnaire (subject's perception of how old they think they look following the treatment) at all timepoints after LCL treatment, will be categorically summarized by proportion of subjects with a given response.

6.5.3.4 Descriptive Statistics and Change from Baseline

Responses to the FASE questionnaire at all timepoints after LCL treatment, actual age, number of years older, younger will be descriptively summarized.

Transformed scores for the FACE-Q^{TM} Appraisal of Lines: Crow's Feet will be summarized using descriptive statistics for continuous variables.

6.5.4 Adjustments for Covariates

The analysis of the primary endpoint requires a regression model to be run, where the baseline IGA-LCWS severity and study site are included in the model as covariates.

[redacted]

6.6 Safety Analyses

Safety summaries and analyses will be performed on the Safety population and will be presented by cohort and in total across cohorts. Descriptive statistics will be presented to summarize the safety data. By visit safety summaries will use denominators based on the number of subjects with valid observations at that visit unless otherwise specified.

6.6.1 Extent of Exposure

All subjects are planned to receive LCL treatment. The dosage of investigational product injected and the dose of investigational product injected at each of the injection sites will be summarized overall and by summary cohort for each administration using descriptive statistics (number of non-missing observations, mean, median, first and third quartiles, minimum, maximum, and standard deviation).

6.6.2 Injection Site Evaluations

The injection site evaluations for LCL will be summarized using number and percentage of subjects with a reaction at any post-treatment visit. In addition, the number and percentage of subjects experiencing an AE of special interest related to LCL injection site reactions will be summarized by summary cohort, system organ class, and preferred term.

6.6.3 Adverse Events

All AEs will be recorded and classified on the basis of MedDRA terminology. All treatment-emergent AEs will be summarized by summary cohort and overall, system organ class, preferred term, severity, and seriousness. When summarizing events by causality and severity by subject, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification. In the case of missing AE severity or relationship, the most severe/highest relationship will be imputed. Additionally, some summaries will present the number of AEs as well as incidence.

An overall summary of treatment-emergent AEs (TEAEs) will be provided. The number and percentage of subjects experiencing an AE, an SAE, a related AE, a related SAE, an AE of special interest, an AE leading to study discontinuation, and an AE resulting in death will be summarized.

All information pertaining to AEs noted during the trial will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding trial drug, corrective treatment, outcome, and drug relatedness. The event onset relative (in number of days) to the date of treatment for LCL, as well as to the date of last treatment administration prior to the event, will be provided. In addition, a list of adverse events that lead to the subject's premature discontinuation of the trial will be provided. Serious adverse events (SAEs) will be listed by subject.

6.6.4 Laboratory Tests

6.6.4.1 Clinical Safety Laboratory Parameters

Laboratory test results will be summarized with descriptive statistics by visit. Change from baseline to post-baseline visits will be summarized for continuous test results. A summary of abnormal urinalysis incidence will be presented displaying normal, abnormal (not clinically significant), and abnormal (clinically significant) results.

Shift tables will be presented to summarize laboratory test results at Baseline and Final Evaluation Visit. Normal ranges established by the central laboratory will be used to determine shifts. A listing of all out-of-range laboratory test results at any evaluation will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by the investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

6.6.4.2 Pregnancy Tests

Urine pregnancy tests will be presented in data listings for all treated subjects in the category of woman of child-bearing potential.

[redacted]

[redacted]

[redacted]

[redacted]

6.6.6 Vital Signs and Physical Examination

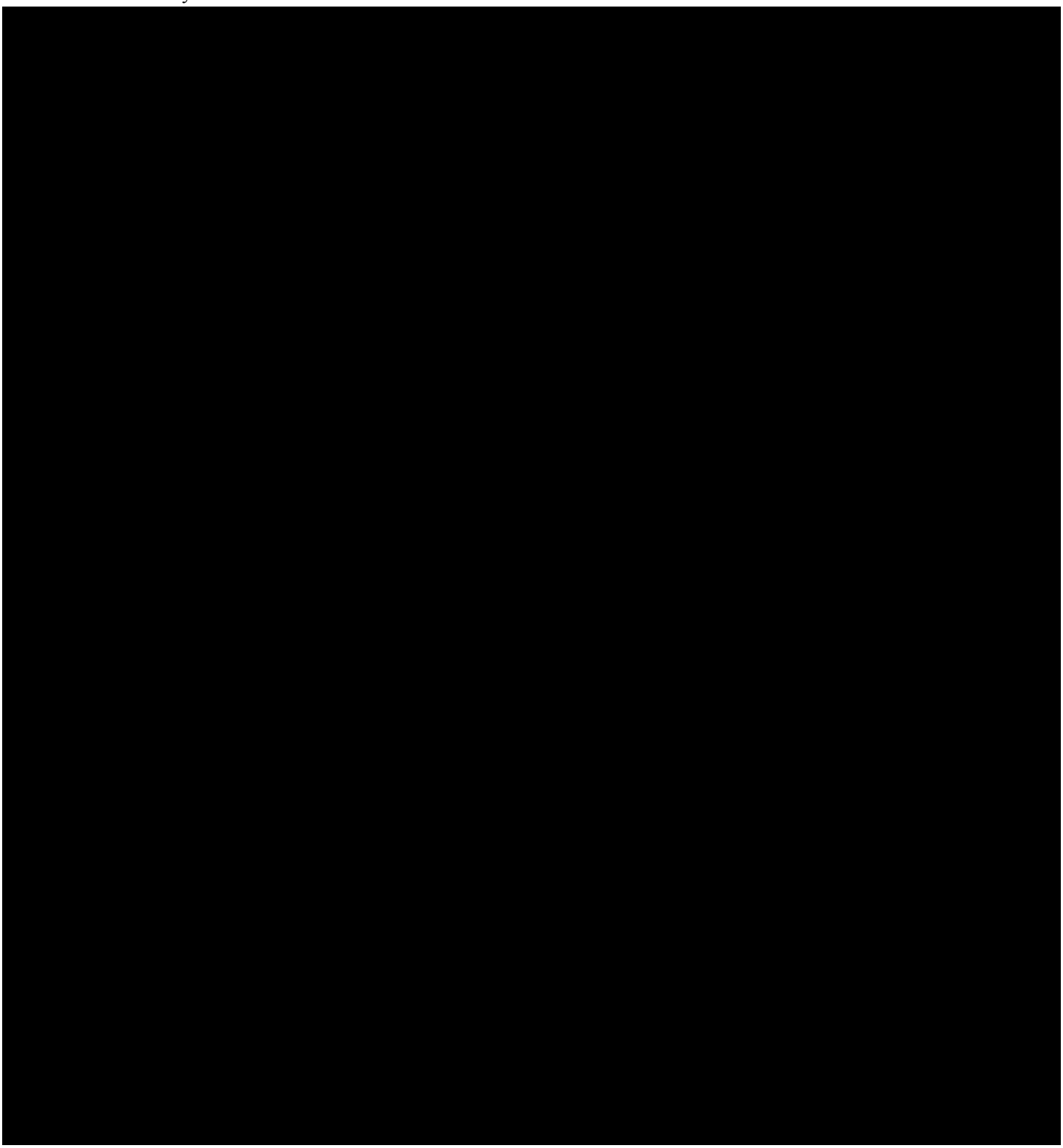
Vital signs and ECG parameters will be summarized by cohort with descriptive statistics by visit. Vital signs and ECG parameters will summarize the actual value as well as the change from baseline for each visit for continuous parameters.

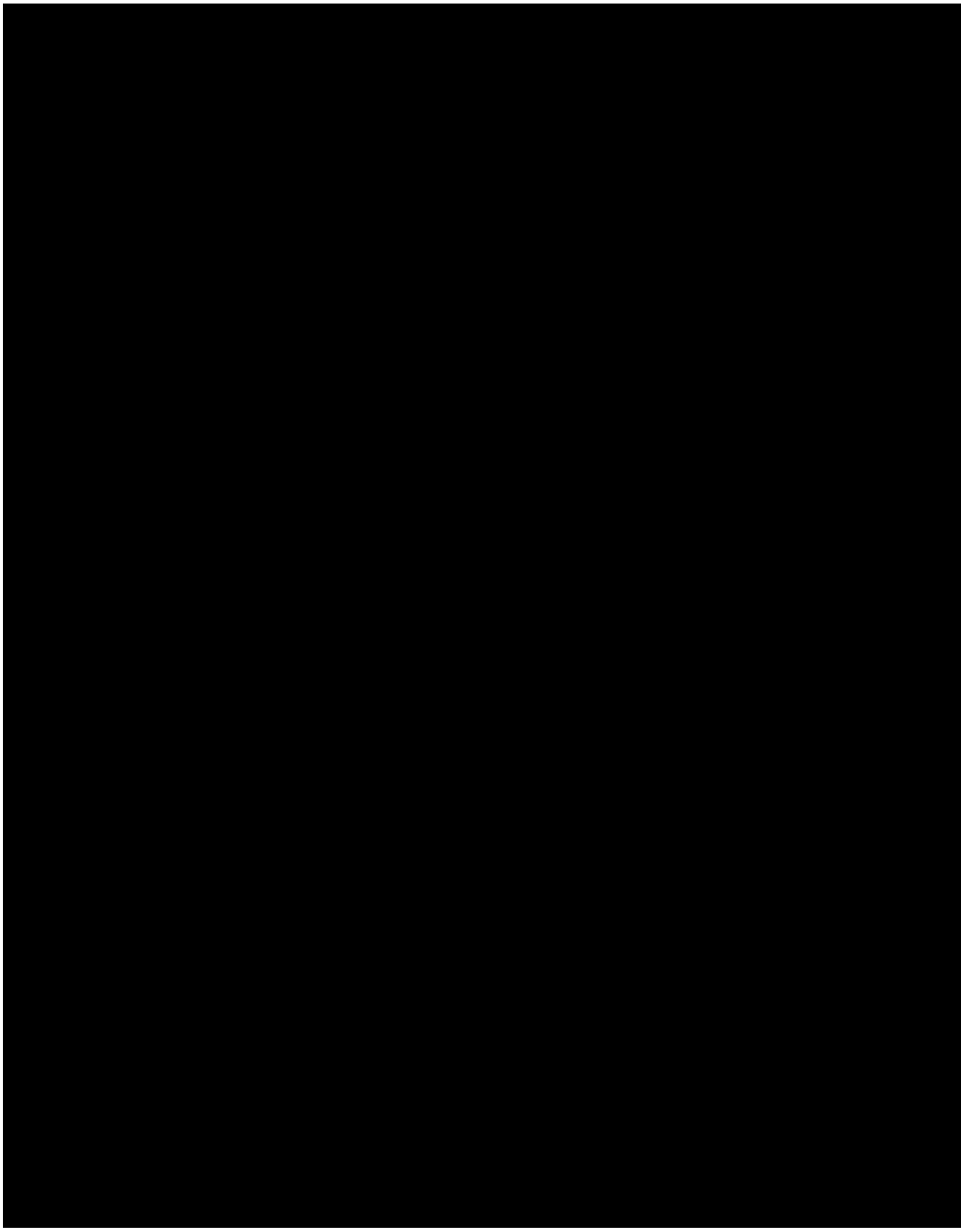
Abnormal findings from the physical examination will be summarized by body system and cohort using number and percentage of subjects with a normal, abnormal and clinically significant, or abnormal and not clinically significant result.

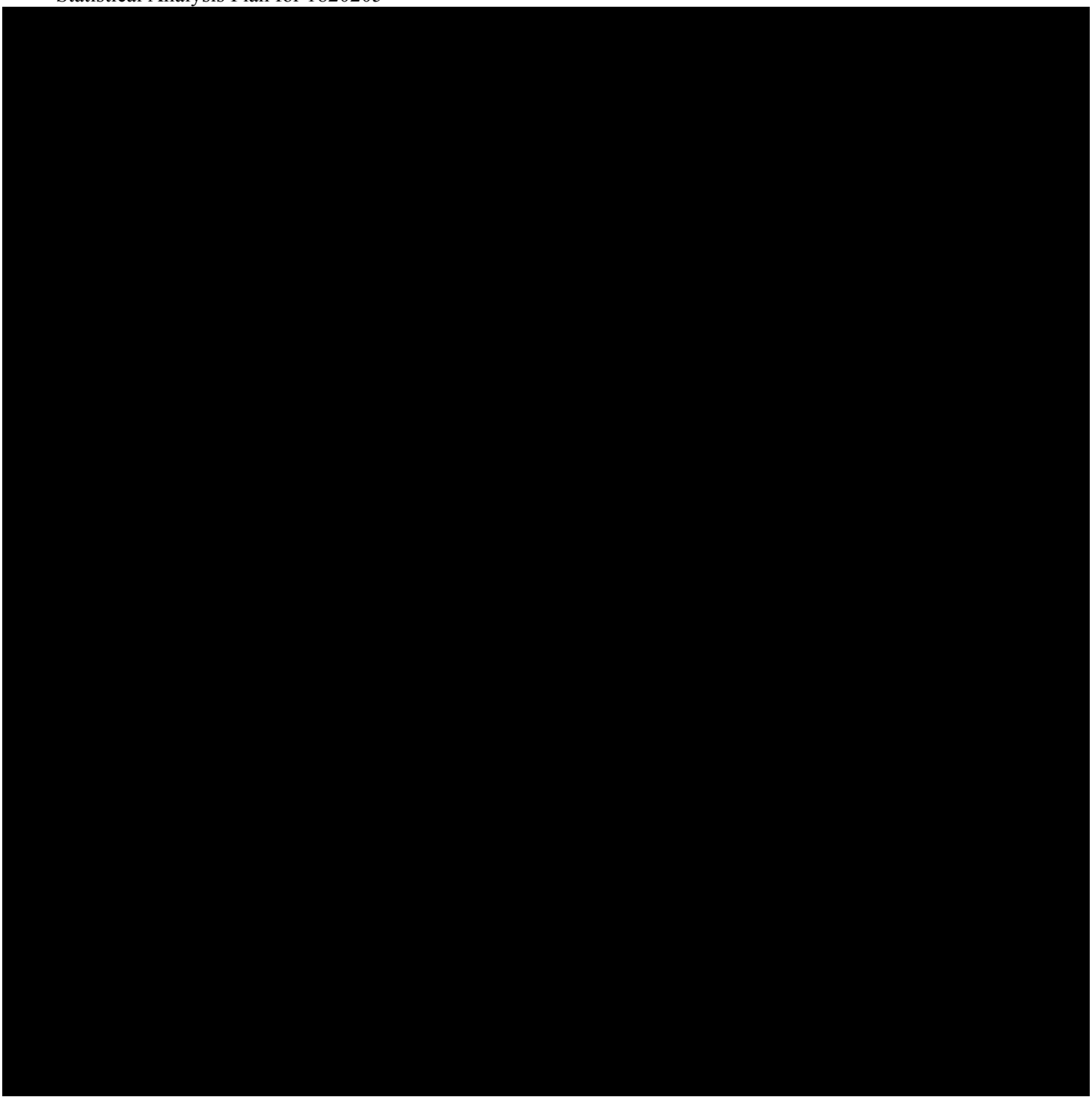
[redacted]

[redacted]

[redacted]

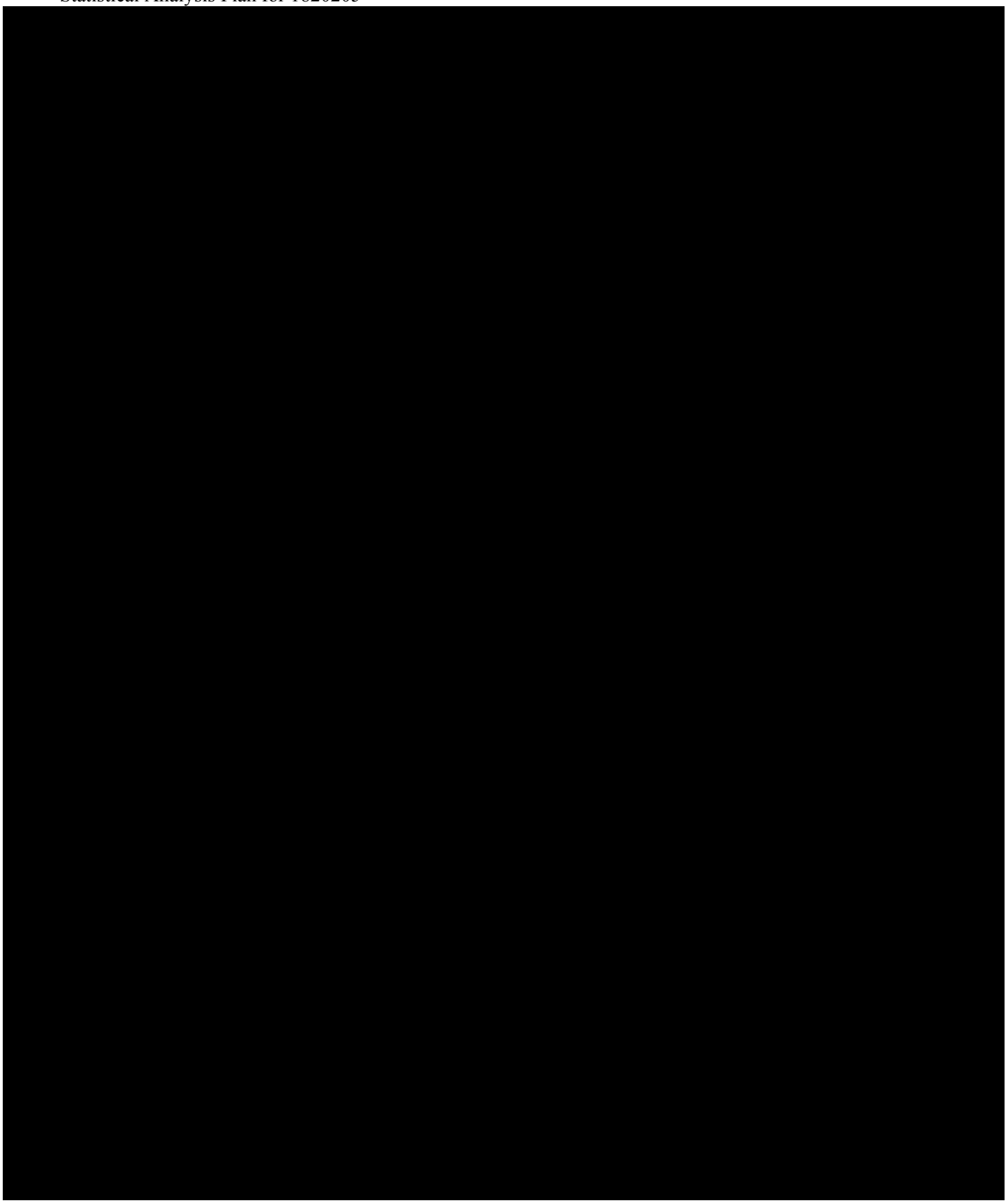




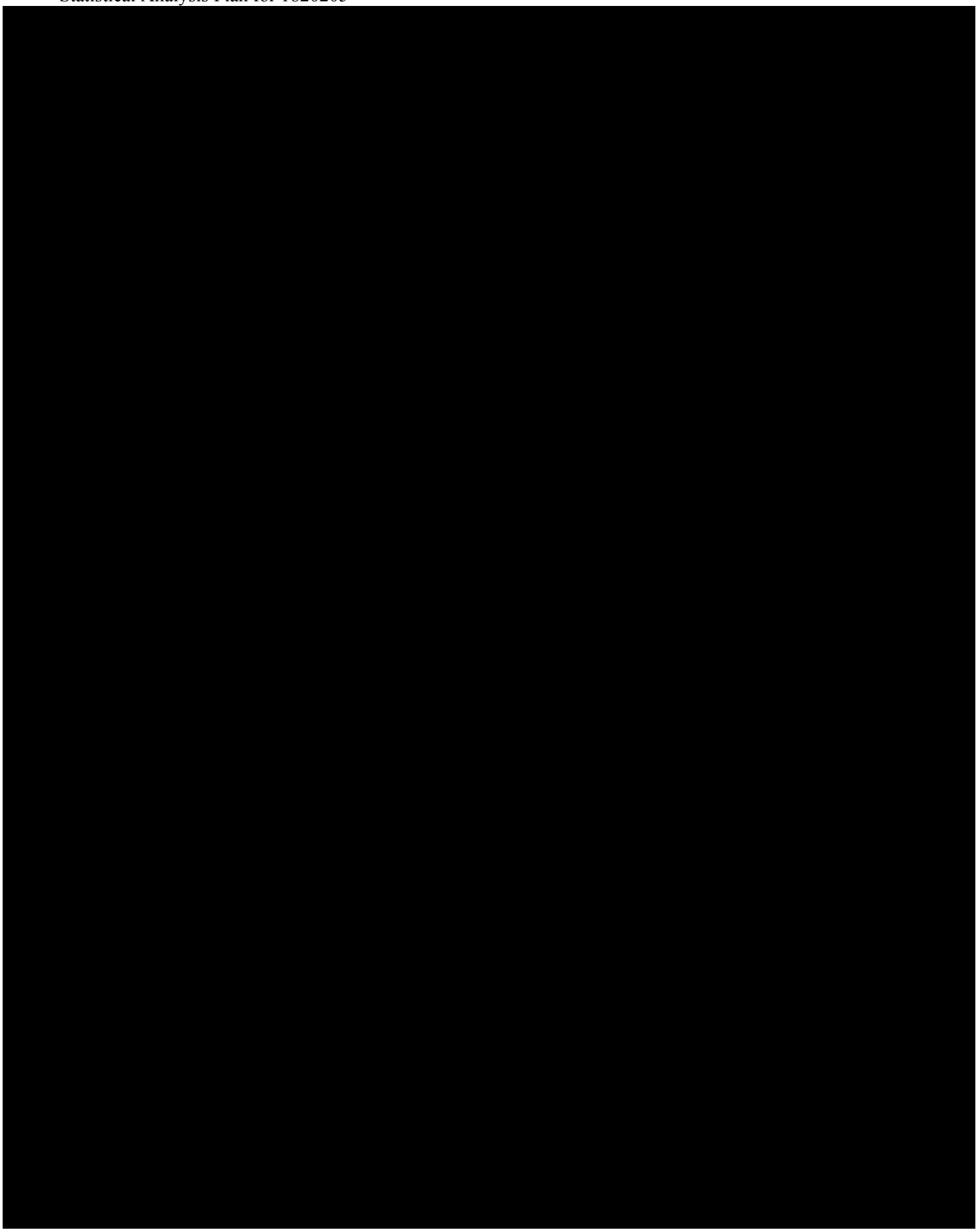


[redacted]

[redacted]



[redacted]



[redacted]