STATISTICAL ANALYSIS PLAN

Protocol Number:	1720201
Title:	A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis
Study Phase:	2
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA 94560
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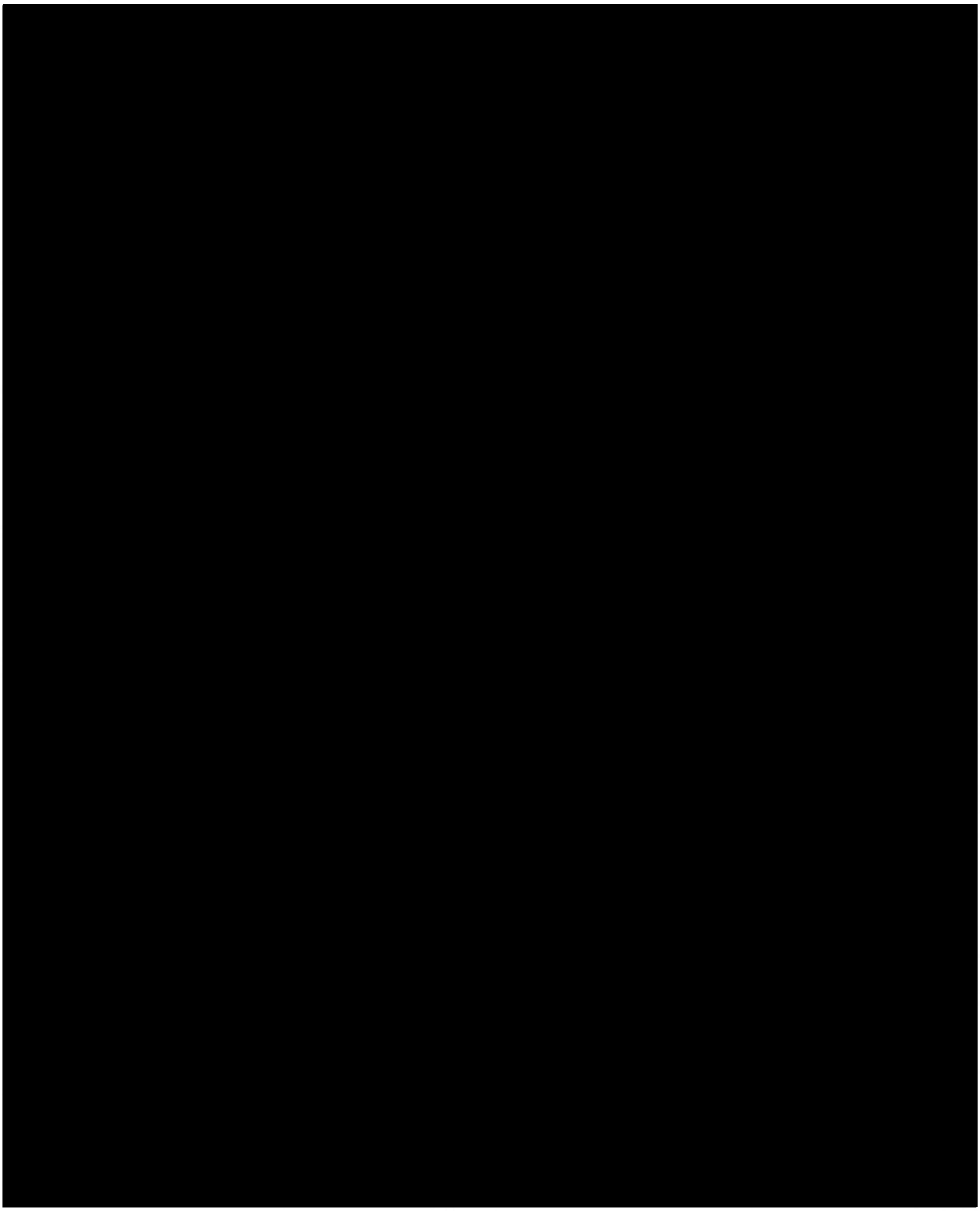

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
AOFAS	American Orthopaedic Foot and Ankle Score
BoNTA	Botulinum Toxin Type A
cm	Centimeter
CRF(s)	Case Report Form(s)
ECG	Electrocardiogram
FADI	Foot and Ankle Disability Index
GLM	Generalized Linear Model
ITT	Intent-to-treat
kDa	Kilodalton
LOCF	Last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mm	Millimeter
PFPS	Plantar Fasciitis Pain and Disability Scale
PI	Principal Investigator
PP	Per-Protocol
PROMIS	Patient Reported Outcomes Measurement Information System
Revance	Revance Therapeutics, Inc.
RT002	daxibotulinumtoxinA for injection
RTP004	Revance absorption enhance peptide
SAE	Serious Adverse Event
SAS	Statistical Software from SAS Institute Inc.
SPT	Serum Pregnancy Test
UPT	Urine Pregnancy Test
US	United States of America
VAS	Visual Analog Scale
WOCBP	Women of Child-Bearing Potential

1 INTRODUCTION

Ten percent of the general population experiences heel pain or plantar fasciitis during their lifetime. [1] Plantar fasciitis causes significant discomfort and negatively impacts the health-related quality of life of affected individuals. Botulinum toxin was theorized over a decade ago to have potential efficacy in the management of plantar fasciitis. [2] Botulinum toxins have been used as injectable agents in the management of refractory plantar fasciitis without complication and with demonstrable clinical efficacy.

[redacted]

This statistical analysis plan (SAP) describes the objectives of the study and the efficacy and safety assessments that are collected. The primary, secondary, and exploratory efficacy endpoints and the safety 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 following the text of the SAP.

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary study objective is to compare the safety and efficacy of daxibotulinumtoxinA for injection versus placebo for managing plantar fasciitis as measured by the reduction in the visual analog scale (VAS) for pain for the foot at Week 8.

[redacted]

3 Overall Study Design and Plan

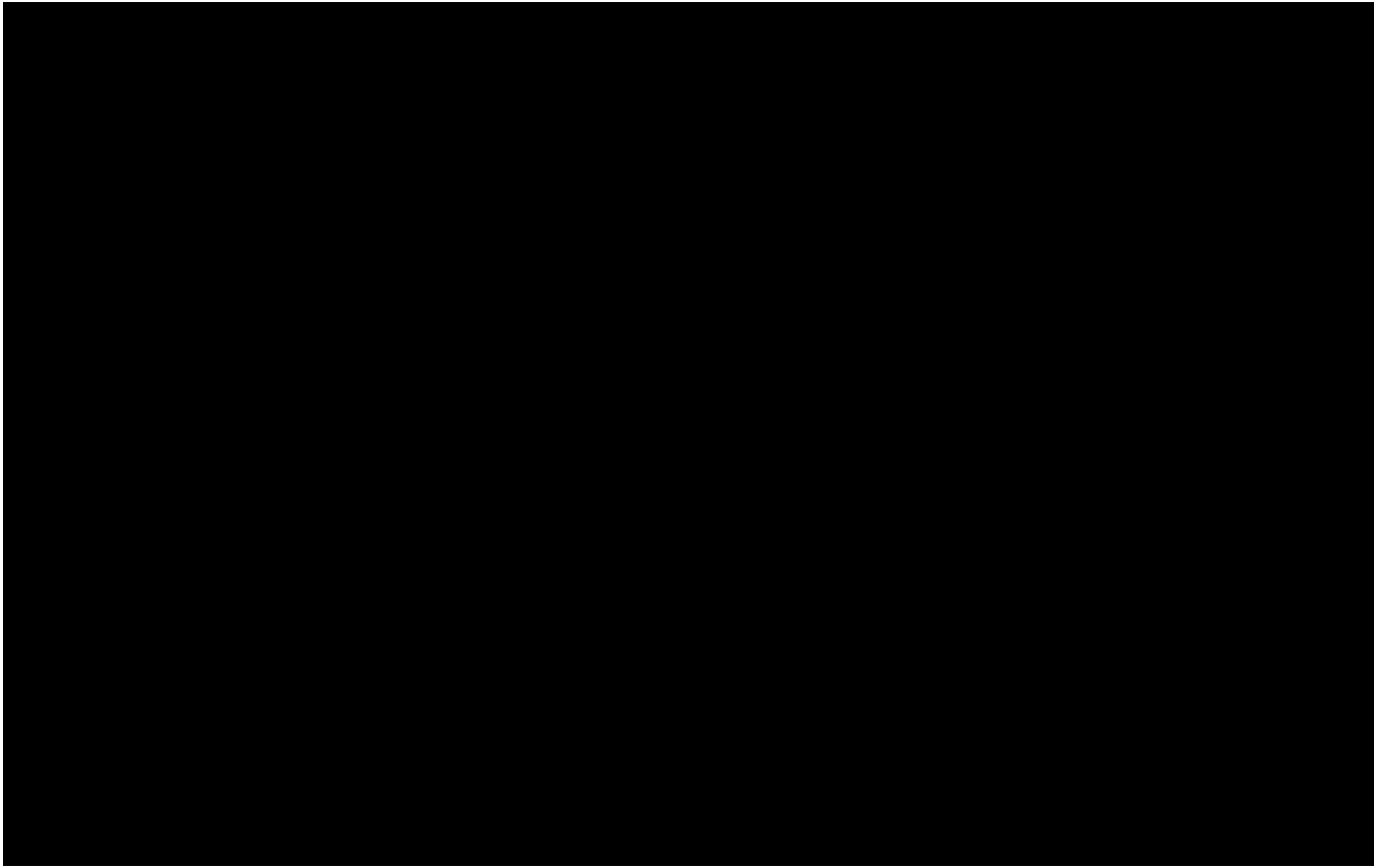
3.1 Study Design

The study is designed as a phase 2, prospective, randomized, placebo-controlled, double-blinded clinical trial to compare daxibotulinumtoxinA for injection and placebo injections for the management of plantar fasciitis signs and symptoms.

Approximately 60 subjects, from 5 sites in the United States, 18-65 years of age, [redacted]

The study duration for each participant is up to approximately five (5) months (up to four [4] weeks for Screening, a single Injection day, and up to 16 weeks of Follow-up). [redacted]

A participant is considered to have completed the study if he or she has completed all visits of the study including the last visit or the last scheduled procedure (See Table 3.1-1 for the complete schedule of assessments). The end of the study is defined as completion of the last visit or procedure in the trial globally.



3.1.1 Determination of Sample Size

With a total of 60 subjects (30 per group) and assuming a drop-out rate of no more than 20%, [redacted]

3.1.2 Treatments Administered

Approximately 60 adult subjects with a diagnosis of unilateral plantar fasciitis, refractory to conservative treatment, will be enrolled.

[redacted]

[redacted]

3.2 Efficacy and Safety Assessments

3.2.1 Efficacy Assessments

The efficacy assessments used in this study are:

- Visual Analog Scale (VAS) for Pain: The VAS for pain is a continuous scale self-completed by the respondent comprised of a horizontal or vertical line anchored by "no pain" (score of 0) and "worst pain" or "worst imaginable pain" (score of 100 [100-mm scale]).

[redacted]

3.2.2 Safety Assessments

Safety assessments include the physical examination; pregnancy testing for women of child-bearing potential (WOCBP); height, weight and other vital signs; 12-lead electrocardiograms; clinical laboratory evaluations; injection site evaluations, foot and ankle examinations, and assessments of adverse events.

3.2.2.1 Adverse Events

All adverse events (AEs) will be recorded and classified in accordance with MedDRA terminology. Severity, frequency, and relationship of AEs to study intervention will also be collected. AE severity will be graded as mild, moderate, or severe, as defined in Section 8.4.3.1 of the protocol. Relationship of an AE to investigational product will be assessed as definite, probable, possible, or unrelated, as defined in Section 8.4.3.2 of the protocol. AEs with an onset on or after the date and time of study treatment will be considered as Treatment-emergent.

[redacted]

3.2.2.2 Clinical Laboratory Data

Blood samples will be collected for clinical laboratory (chemistry, hematology, urinalysis) at Screening, Weeks 2 and 16/Early Termination visits. [redacted]

Table 3.2.2.2-1 Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis	Additional Tests
Hemoglobin	Glucose [a]	Specific gravity	[redacted]
Hematocrit	Total bilirubin	pH	
Leukocyte count (total)	Alanine aminotransferase	Glucose	
Leukocyte count (differential)	Aspartate aminotransferase	Protein	[redacted]
Red blood cell count	Alkaline phosphatase	Blood	
Platelet count	Blood urea nitrogen	Bilirubin	[redacted]
	Pregnancy (WOCBP at Screening)	Ketones	
	Sodium		
	Potassium		
	Chloride		
	CO2		
	Creatinine		
	Calcium		
	Protein		
	Albumin		
	Anion GAP		
	GFR		

[redacted]

a. Clinical laboratories need not be fasting

3.2.2.3 Height, Weight, Vital Signs

Height will be collected only at the Screening visit. Weight and 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 Visit, Injection Visit (pre- and post-treatment), Weeks 1, 2, 4, 8, and 16/Early Termination, [redacted]

3.2.2.4 Physical Examination

A full physical examination, including neurological examination of the face, general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, and extremities will be conducted at Screening and pre-treatment at the Injection visit. Significant

physical examination findings that are present prior to investigational product administration are to be included on the Medical History page.

At post-treatment visits, the physical examination may be abbreviated, as deemed medically appropriate at the discretion of the Investigator. Significant physical examination findings which meet the definition of an adverse event will be recorded on the adverse event page post-treatment.

3.2.2.5 12-Lead ECG

At Screening, Week 2, and Week 16/Early Termination, a single standard supine 12-Lead ECG will be obtained after a subject has rested quietly for at least 10 minutes. The ECG data will be submitted to a central reader for measurement.

3.2.2.6 Injection Site Evaluation

The injection sites will be evaluated before injection and post-injection at Injection Visit (Day 1; to determine if there is an immediate reaction to the investigational product), and at follow-up Visits (Weeks 1, 2, 4, 8, and 16/Early Termination visit, if applicable). The assessment will be done as a global evaluation of the four injection sites reporting the presence or absence of: erythema, edema, burning or stinging (as described by the subject), itching (as described by the subject), bruising and drainage.

3.2.2.7 Foot and Ankle Examination

Examination for the foot includes ankle, toe, and subtalar range of motion, foot motor strength, location of pain, and examination of the heel fat pad and Tinel's sign. This will be performed at Screening, pre-treatment Injection, Weeks 1, 2, 4, 8, and 16/Early Termination visits. The presence of toe deformities, bunions, ulcers, and/or sores will be documented. The feet will be examined for signs of swelling, pitting edema, infection, or vascular abnormalities.

3.2.2.8 Concomitant Medications

Concomitant medications are any prescription or over-the-counter preparations used by subjects during participation in the trial. Use of concomitant medications will be recorded, beginning at the Screening Visit until the Week 16/Early Termination visit. The dose and dosing regimen of all prescription and non-prescription therapies and medications, including herbs, vitamins, or other nutritional supplements administered will be documented.

4 Statistical Methods

All statistical programming will be performed using statistical analysis system (SAS) version 9.3 or higher.

4.1 Analysis Populations

4.1.1 Intent-to-Treat Population

All subjects who are randomized will be included in the Intent-to-Treat (ITT) population. All planned statistical analysis will be done on the ITT population. This is the primary analysis for the study.

4.1.2 Modified Intent-to-Treat Population

All subjects who received the study treatment (daxibotulinumtoxinA for injection or placebo) will comprise the modified ITT population (mITT), and will be grouped according to each subject's randomization assignment.

4.1.3 Per Protocol Population

The Per-Protocol (PP) population will include subjects from the mITT population who do not have any major protocol violations. [redacted]

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

[redacted]

[redacted]

4.1.4 Safety Population

All subjects who are randomized, receive treatment, and have provided at least one post-treatment safety assessment will be included in the Safety population. The summaries will be by documented treatment actually received.

4.2 Subject Disposition

The number and percentage of patients who have signed informed consent, been randomized, received treatment, and completed key visits will be tabulated by treatment group overall and by trial center (or pooled center, as appropriate) and included in a listing. Reasons for not completing the study will also be tabulated by treatment group and overall and by trial center using numbers and percentages; this data will also be included in a listing. For those patients who are considered to have failed screening, the reason(s) for failure will be provided in a listing.

The number and percentage of patients included and excluded from the analysis populations (ITT, PP and safety) will be tabulated overall and for each treatment group. Reason(s) for exclusion from each population will be summarized and listed.

[redacted]

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

4.3 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics by treatment group and overall. Continuous variables will be summarized using the number of non-missing observations, mean, standard deviation, median, minimum and maximum. Categorical

data will be summarized using the number and percentage of patients in each category. Demographic data include age, sex, race and ethnicity. Age in years will categorized as <30, 30-<40, 40 to <50, 50 to <60, and >=60 for summarizing by treatment group and overall. Baseline characteristics include the Foot and Ankle Physical Examination assessments of the efficacy questionnaires: AOFAS, FADI, PROMIS, and PFPS. Summaries will be produced for the ITT and PP populations by randomized treatment; and, selected summaries will be produced for the Safety population by actual treatment received.

4.4 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 by treatment group, system organ class, and preferred term, and will be listed.

4.5 Prior and Concomitant Medications

Prior therapies/medications recorded at Screening but no longer being taken, and concomitant therapies/medications recorded at Screening and still being taken or being taken at each trial visit, will be coded using the World Health Organization (WHO) drug dictionary and summarized by treatment group and overall, Anatomical Therapeutic Chemical (ATC) second level term, and preferred name for the Safety population. Prior and concomitant medications will be summarized separately.

4.6 Efficacy Analyses

Data listings and descriptive statistics will be produced for all endpoints at all timepoints by treatment group.

[redacted]

[redacted]

[redacted]

4.6.1.1 Primary Endpoint

The change from baseline in the VAS for pain for the affected foot at Week 8, in the ITT Population is the primary endpoint. [redacted]

[redacted]

[redacted]

[redacted]

4.6.1.4 Sensitivity Analyses

As a sensitivity analysis to check the impact of major protocol violations on study results, the primary and secondary efficacy outcome measures will also be analyzed on observed data from all subjects in the per-protocol (PP) population. As well, to check the robustness of results using the LOCF approach, analysis using multiple-imputation for the missing data on ITT population

will be used as sensitivity analysis. Thus, each primary and secondary endpoint will have two additional sensitivity analyses.

[redacted]

4.7 Safety Analyses

Safety summaries and analyses will be performed on the Safety population. Descriptive statistics will be presented to summarize the safety data.

4.7.1 Extent of Exposure

All subjects receive one administration of investigational product. The total volume of investigational product injected and the volume of investigational product injected at each of the injection sites will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum).

4.7.2 Adverse Events

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 study drug, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to the date of first study treatment administration. In addition, a list of subjects who prematurely discontinue from the trial due to adverse events will also be provided.

All treatment-emergent AEs (TEAEs) will be listed and summarized by treatment group, system organ class, preferred term, severity, relationship, and seriousness. Also, serious AEs (SAEs) will be summarized by treatment group, severity, and relationship to study treatment. For summaries, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship or highest severity.

Comparisons between treatment groups will be made by tabulating the frequency of subjects with one or more TEAEs from baseline (post-treatment) to Week 8, as well as from baseline (post-treatment) through the duration of the trial.

[redacted]

The injection site evaluations will be summarized using number and percentage of subjects reporting the presence of each item by treatment group and visit. In addition, the number and percentage of subjects reporting any injection site item will be summarized by treatment group overall, and by visit.

4.7.3 Laboratory Tests

Laboratory test results, actual values and change from screening values, will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, minimum and maximum) for each treatment group at Screening, Visit 4 (Week 2), and the Final Evaluation Visit. Categorical laboratory test results will be summarized using number and percentage of subjects in each category for each treatment group at Screening, Visit 4 (Week 2), and the Final Evaluation Visit.

Shift tables (low, normal, high) will be presented to summarize laboratory test results at Screening and the Final Evaluation Visit. Normal ranges established by the central laboratory will be used to determine shifts.

Urine pregnancy tests will be presented in data listings only.

[redacted]

4.7.5 Vital Signs, Physical Examination, and ECG

Vital signs will be summarized with descriptive statistics for each treatment group by visit.

Significant physical examination findings that are present prior to investigational product administration are to be included on the Medical History page. Significant physical examination

findings which meet the definition of an adverse event will be recorded on the adverse event page post-treatment. Subject's physical examination findings will be provided in a listing.

Descriptive statistics will be used to summarize the overall ECG assessment at baseline, Week 2, and Week 16/Early Termination.

4.8 Statistical/Analytical Issues

4.8.1 Adjustments for Covariates

Baseline values of the efficacy endpoints will be included in models as a covariate for the given endpoint. Site (study centre) will also be included in the model. No other adjustments for covariates are planned.

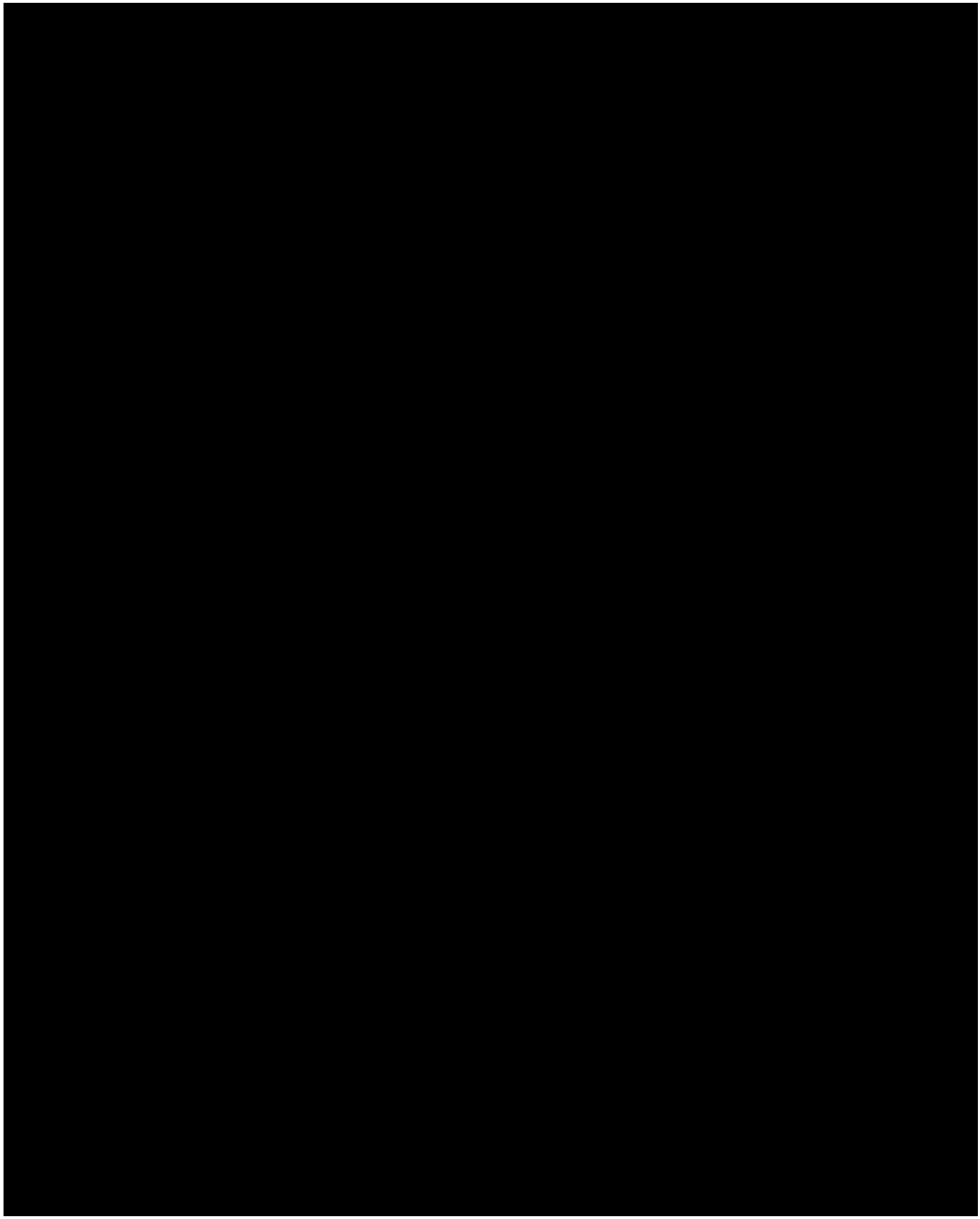
[redacted]

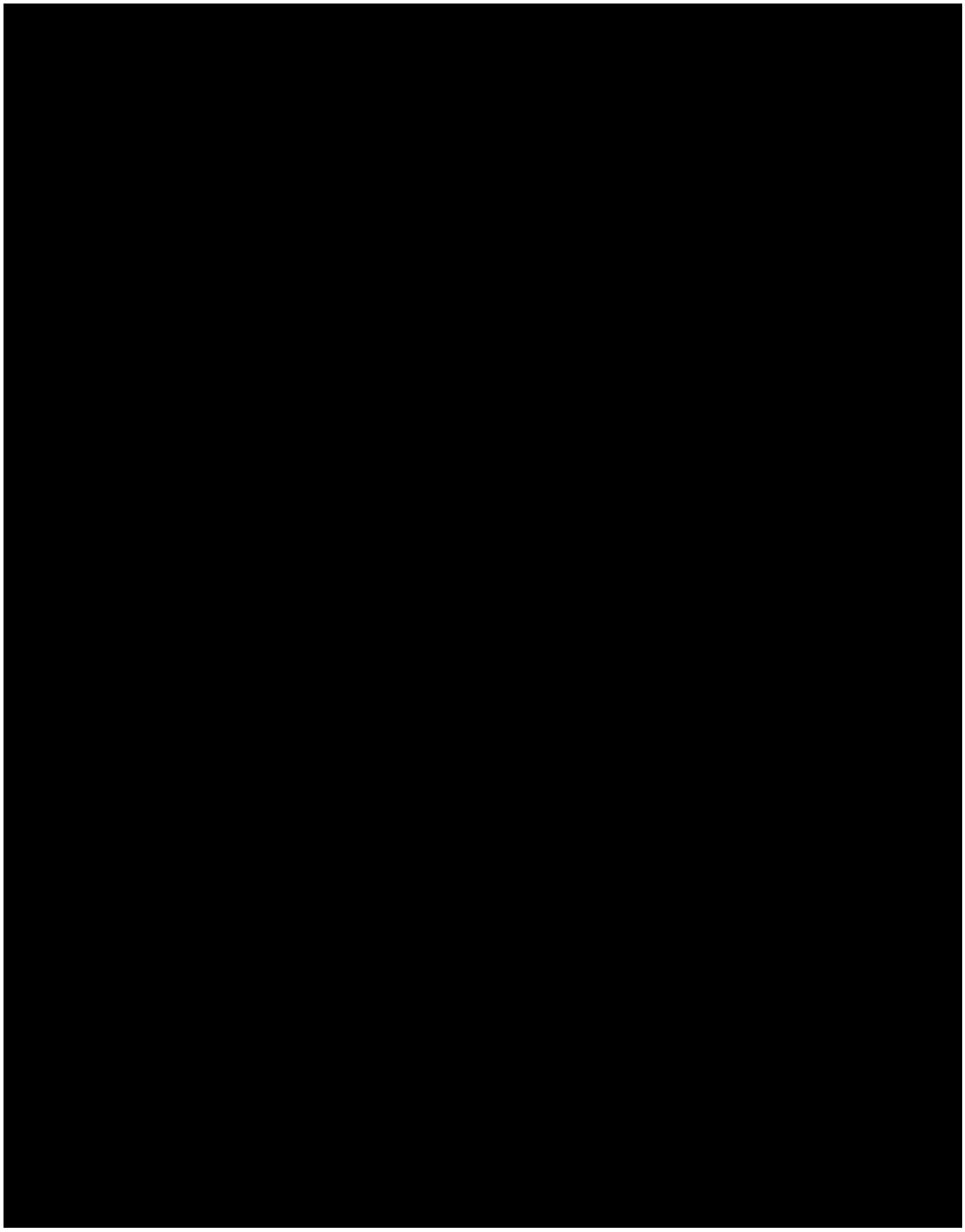
4.8.4 Data Handling Conventions

For all analyses, the protocol-specified Injection Day (also referred to as Injection Visit) will be referred to as Day 1, for compliance with CDISC standards.

[redacted]

[redacted]





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