# A randomized, no-treatment-controlled, evaluator-blinded, multi-center study to evaluate the effectiveness and safety of *Restylane® Defyne* in the chin for augmentation and correction of Chin Retrusion

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GALDERMA

# Galderma Research and Development, LLC

## Protocol Number: 43USCH1702

# Statistical Analysis Plan

Version 1.0

19 September 2018

[redacted]

[redacted]

# TABLE OF CONTENTS

# TABLES

# 1.0 PURPOSE

This SAP describes the methods to be used in the analysis of study data from clinical protocol 43USCH1702 titled "A randomized, no-treatment-controlled, evaluator-blinded, multicenter study to evaluate the effectiveness and safety of Restylane® Defyne in the chin for augmentation and correction of Chin Retrusion" in order to answer the study objective(s), and is based on version 3.0 of the study protocol, dated 05JUL2018.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this study. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

# 2.0 ACRONYMS

Below is the list of acronyms that will be used throughout this document.

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| ATC-4 | Anatomical Therapeutic Chemical 4th level |
| BMI | Body Mass Index |
| BOCF | Baseline Observation Carried Forward |
| CDISC | Clinical Data Interchange Standards Consortium |
| CSR | Clinical Study Report |
| G | Gram |
| eCRF | Electronic Case Report Form |
| ET | Early termination |
| eCTD | Electronic Common Technical Document |
| FST | Fitzpatrick Skin Type |
| GAIS | Global aesthetic improvement scale |
| GCRS | Galderma Chin Retrusion Scale |
| ICH | International Conference on Harmonisation |
| ICF | Informed Consent Form |
| IP | Investigational Product |
| IPR | Independent Photographic Reviewer |
| IRE | Injection Related Events |
| ISO | International Organization for Standardization |
| ITT | Intention-to-treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PP | Per Protocol |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |

| Abbreviation | Description |
|---|---|
| SOP | Standard Operating Procedure |
| TC | Telephone Call |
| TW | Thin Wall |
| WHO | World Health Organization |
| Tx | Treatment |

# 3.0 OVERALL STUDY DESIGN AND OBJECTIVE

## 3.1 Study Objectives

### 3.1.1 Primary Effectiveness Objective

The primary objective of the study is to evaluate the effectiveness of *Restylane® Defyne* versus a no-treatment control in the correction of chin retrusion by comparing response rates, defined by at least 1 point improvement from baseline using [redacted], as assessed by the Blinded Evaluator, at 12 weeks after last injection for the treatment group or after baseline if randomized to no treatment.

### 3.1.2 Secondary Effectiveness Objectives

The secondary objectives of this study are:

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

[redacted]

### 3.1.3 Safety Objectives

The safety objectives of this study are:

i) To evaluate all adverse events (AEs) and pre-defined, injection related events (IREs) reported [redacted]

[redacted]

[redacted]

## 3.2 Study Design and Study Procedures

This is a randomized, evaluator-blinded, parallel group, no-treatment control, multi-center study to evaluate the effectiveness and safety of Restylane® Defyne for chin augmentation and correction of Chin Retrusion.

## 3.3 Treatments and Assignment to Treatments

Approximately 140 subjects, [redacted] will be enrolled and randomized [redacted] of treatment to Restylane® Defyne or no-treatment-control.

[redacted]

[redacted]

# 4.0 GENERAL ANALYSIS CONVENTION

Data collected in this study will be documented using summary tables and subject data listings. Continuous endpoints will be summarized using descriptive statistics, e.g. number of subjects, mean, median, standard deviation, minimum and maximum values. Categorical endpoints will be presented in frequency tables with number and percentage of observations for each level.

Confidence intervals will be two-sided and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two sided.

Study days will be calculated relative to the date of first dose of study product for subjects randomized to Treatment and relative to the date of randomization for subjects randomized to No Treatment. Day 1 will be the first day of study product administration in the study for the subjects randomized to Treatment and the day of randomization for the subjects randomized to No Treatment. The day prior to Day 1 will be Day -1. There will be no Day 0.

Baseline will be the last assessment prior to the first dose of study product for subjects randomized to Treatment and the last assessment prior to the randomization for subjects randomized to No Treatment. For analysis purpose, the date of randomization will be considered as the date of first dose for subjects who are randomized to No Treatment.

Adverse events and Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Mar 2018).

Data for all subjects in the clinical database will be included in the data listings. Calculated (derived) variables will be listed as appropriate. All tables, listings, and figures will be programmed using SAS Version 9.3 or higher. A list of proposed statistical tables, listings, and figures is provided in Section 16.0. Any changes from the SAP will be detailed in the CSR.

[redacted]

# 5.0 ANALYSIS POPULATIONS

The Analysis Populations to be used for the analyses in this study are described below.

## 5.1 Intent-to-Treat (ITT) Population

Includes all subjects who were randomized based on the as randomized principle (i.e. according to the treatment they were randomized to).

## 5.2 Per-Protocol (PP) Population

Includes all subjects in ITT who complete the Week 12 visit without any deviations considered to have substantial impact on the primary effectiveness outcome.

## 5.3 Safety Population

Includes all subjects who were treated with *Restylane® Defyne* or randomized to no treatment control group. Subjects are analyzed based on the as treated principle (i.e. according to the treatment actually received).

The primary and secondary effectiveness analyses will be performed using the ITT analysis set. The primary and the first secondary effectiveness analysis will be repeated using the PP analysis set if there is at least a 10% difference in the number of subjects between the PP and ITT sets. The safety evaluations will be performed based on the safety analysis set.

# 6.0 SUBJECT DISPOSITION

Subject disposition will be summarized in a table. The number of subjects screened and randomized will be presented. The number of subjects in the Safety, ITT and PP populations will be summarized. The number and percentage of subjects in the ITT population who complete the study will be summarized, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the eCRFs.

Data will be summarized by treatment group and overall except for the number of subjects screened.

All withdrawn subjects will be listed individually, including at least subject number, date and reason for withdrawal, and last visit performed.

Inclusion/exclusion data will be presented by subjects in a data listing.

# 7.0 PROTOCOL DEVIATIONS

Protocol deviations will be presented by subject in a data listing. Subjects with protocol deviations will be listed individually, including subject number and observed deviation. Depending on the seriousness of the deviation, subject

might be excluded from the PP population, which shall be documented prior to database lock.

# 8.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

## 8.1 Demographic and Baseline Characteristics

Demographic endpoints, baseline assessments, and subject characteristics will be presented based on the ITT population using descriptive statistics by treatment, as appropriate. Some of the variables to be summarized are described below (other variables maybe added dependent on final eCRF):

[redacted]

**Table 1: Fitzpatrick Skin Types (FST)**

| Skin type | Skin color | Skin characteristics |
|---|---|---|
| I | White; very fair; red or blond hair; blue eyes; freckles | Always burns, never tans |
| II | White; fair; red or blond hair; blue, hazel or green eyes | Usually burns, tans with difficulty |
| III | Cream white; fair with any eye or hair color; very common | Sometimes mild burn, gradually tans |
| IV | Brown; typical Mediterranean Caucasian skin | Rarely burns, tans with ease |
| V | Dark brown; Middle Eastern skin types | Very rarely burns, tans very easily |
| VI | Black | Never burns, tans very easily |

Continuous variables will be summarized with descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Categorical variables will be summarized using counts and percentages.

Demographic and baseline characteristics will be presented by treatment and subject in data listings.

### 8.2 Medical History

History of relevant surgical events and medical conditions, including any prior dermatological procedures or implants, are collected.

Medical history will be summarized by individual treatment group and overall for the ITT population as given below:

[redacted]

## 9.0 EFFICACY VARIABLES

### 9.1 Primary Efficacy Variable

Response rates, where a responder is define [redacted]

[redacted]

### 9.2 Secondary Efficacy Variables

The secondary efficacy variables are:

[redacted]

[redacted]

# 10.0 EFFICACY ANALYSIS

All efficacy variables will be summarized at each scheduled visit for the ITT population. Categorical variables will [redacted]

| GALDERMA | Title<br>**43USCH1702 Statistical Analysis Plan** | Doc id<br>[redacted] |
|---|---|---|

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Version: *1.0*

[redacted]

[redacted]

## 10.2 Secondary Efficacy Analysis

[redacted]

[redacted]

[redacted]

[redacted]

# 11.0 STATISTICAL/ANALYTICAL ISSUES

## 11.1 Handling of Dropouts or Missing Data

Number of missing values will be summarized and reported as appropriate.

For ITT analysis [redacted]

## 11.2 Pooling of Centers in Multi-Center Studies

There will be no pooling of centers.

## 11.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

## 11.4 Examination of Subgroups

[redacted]

## 11.5 Interim Analysis and Data Monitoring

There is no interim analysis planned for this study.

# 12.0 EXTENT OF EXPOSURE

Data of extent of exposure and treatment procedure will be summarized for initial treatment, optional touch-up (only for subjects randomized to treatment), optional initial treatment (only for subjects randomized to no treatment), and optional re-treatment (only for subjects randomized to treatment) separately for safety population. Following parameters will be summarized for extent of exposure:

- [redacted]

[redacted]

Extent of exposure data will be presented by subject in data listings.

Following parameters will be summarized for treatment procedure:

[redacted]

Procedural Anesthetics and Injection Concomitant Procedures data will be presented by subject in data listings.

# 13.0 SAFETY ANALYSIS

The safety endpoints include:

- Evaluation all adverse events (AEs).
- Pre-defined, injection related events (IREs) reported during the first 4 weeks after treatment as recorded in the subject diary.
- Presence of any unexpected lumpiness or non-uniform density by palpation of the chin at each physical follow-up visit.
- Presence of any mass formation in the chin at baseline and at each physical visits thereafter.
- Presence of abnormal lower lip movement, function, and sensation (on three different locations) according to pre-defined methods, at baseline and at each physical follow-up visit.
- Presence of abnormal chin function and sensation (on three different locations) according to pre-defined methods, at baseline and at each physical follow-up visit.

## 13.1 Adverse Events

Adverse events (AEs) will be summarized for the safety population. All AEs will be coded using MedDRA and presented by MedDRA system organ class (SOC), preferred term (PT), and treatment.

Only AEs occurring after first injection for subjects randomized to Treatment or after randomization for subjects randomized to No Treatment will be included in analysis. AEs occurring before, if any, will only be listed in subject data listings.

All AE endpoints will be summarized by treatment as follows:

i) No treatment at baseline, includes subjects randomized to No Treatment up until the time of their first injection.

ii) Initial treatment with Restylane Defyne, includes subjects randomized to Defyne (after their first treatment up until their

optional retreatment) pooled with the controls (i.e., subjects randomized to No Treatment) after their optional initial treatment.

iii) Retreatment with Restylane Defyne, includes subjects randomized to Defyne after their optional retreatment.

[redacted]

A summary of AEs will be provided, which will include:

i) number of subjects with at least one AE and number of events (in total as well as serious AEs)
ii) number of subjects with at least one AE, related to study product or injection procedure, and number of events (in total as well as serious AEs)
iii) number of subjects with at least one AE, unrelated to both study product and injection procedure, and number of events (in total as well as serious AEs)
iv) number of subjects who did not have an AE

AEs will be summarized by SOC, PT, and severity.

The number of subjects with AEs related to study product or injection procedure as well as the number of events will be summarized by SOC, PT, and severity. Untreated subjects in control group cannot have a related AE and hence cannot be included in this table.

In addition, for related AEs, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, SD, min, max and median.

Time to onset of an AE will be derived as the start date minus the date of most recent treatment. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment.

Duration of an AE will be derived as the stop date minus the start date + 1. If the start date is missing, it will be assumed that the AE started on the day of most recent treatment. Missing stop date will not be imputed and therefore no duration will be calculated in these cases. Instead, the number of AEs that were ongoing at the end of the study will be given.

If a subject has more than 1 AE of the same PT and there are different grades of severity, only the highest grade will be represented in the summary of severity. If the severity assessment is missing, the highest level of severity will be assumed.

Each AE will be assessed for relatedness to the study product and for the injection procedure. The Investigators will be asked to indicate a response to each of the following questions in the eCRF:

[redacted] "Do you consider that there is a reasonable possibility [redacted]

Action taken for related AEs will also be summarized.

To evaluate consistency of the results across different subgroups, AEs will also be analyzed across different subgroups as described in the exploratory objectives (see Section 3.1.4).

All reported AEs will be listed in data listings including time to onset, duration of AE and timing of the AE. Timing would be the variable indicating whether the AE occurred after no treatment, initial treatment, or optional retreatment.

By-subject listings also will be provided for all subjects (safety population) for the following: AEs related to study product or injection procedure, AEs resulting in discontinuation of study product, and serious AEs.

## 13.2 Pre-defined, expected, post-treatment events

The local tolerability is evaluated by subject in a 28-day diary for the chin, starting on the day of treatment. The presence of pre-defined expected post-treatment events, i.e. bruising, redness, swelling, pain, tenderness, lumps/bumps, itching, and other are assessed for the treated area.

Diary data will be counted and displayed separately from other AE data.

Number and percentage of subjects reporting each pre-defined, expected, post-treatment symptoms, as collected in the 28-day diary, will be presented in total and by maximum severity. Number of days with the event will be presented by treatment group and category: 1-3, 4-7, 8-14, and 15-28.

The local tolerability data will be presented by treatment and subject in data listing.

## 13.3 [redacted]

assessed as "Abnormal" and is reported as an AE if confirmed by the [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## 13.7 Laboratory Assessments

For all women of childbearing potential, a urine pregnancy test will be performed at screening and all injection visits prior to treatment.

The pregnancy test data will be presented by treatment and subject in data listing.

### 13.8 Concomitant Medications and Concomitant Procedures/ Treatments

The number and percentage of subjects reporting concomitant medications will be summarized by treatment. In addition, the number and percent of subjects reporting concomitant medication, and the number of drugs (total number and the number of ongoing drugs), will be summarized by reason. The same summary will be done for concomitant procedures/treatments. Also, the number and percentage of the subjects who took each medication will be tabulated by WHO Drug Dictionary Anatomical Therapeutic Chemical 4thlevel (ATC-4) and preferred name for concomitant medications. If the 4th level term is not available, the next available level (e.g., ATC-3) will be used. A subject will only be counted once within each ATC-4 code and within each preferred name. Concomitant medications that started due to an AE will be summarized separately.

All concomitant medication and concomitant procedures/treatments data will be presented by treatment and subject in a data listing.

## 14.0 QUALITY CONTROL

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).

All analyses will be performed using SAS® Version 9.4 (or later). Advanced Clinical will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses. Galderma or its designee will review all tables, listings, and figures prior to final database lock. All final SAS programs and associated output files will be transferred to Galderma in agreed-upon format at project completion.

## 15.0 TABLES AND LISTING CONVENTIONS

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with Galderma. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by Galderma, the term 'subject' will be used in all tables and listings, in accordance with Clinical Data Interchange Standards Consortium (CDISC) standards.

The general layout of tables and listings will be as follows:

[redacted]

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footers, in accordance with electronic Common Technical Documents (eCTD) guidelines. Font will be Courier New, unless otherwise specified, with a 10-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e., number of decimal places) for presentation of descriptive statistics will be made by Galderma after review of draft statistical tables and before database freeze.

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footers. Data listings will provide all data either collected on the corresponding eCRF page or loaded directly into the database, unless otherwise indicated. If there are too many fields to be fit into a single page, data should be grouped logically and the listings will be generated as Part I, Part II, etc.

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with SAEs) and no subjects meet the condition, the data listing will so indicate.

The sort order for data presented in data listings will be subject number, unless otherwise requested by Galderma. Within a subject, data will be listed in

chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.

# 16.0 LIST OF STATISTICAL TABLES, LISTING AND FIGURES TO BE PROGRAMMED

## 16.1 Statistical Tables

[redacted]

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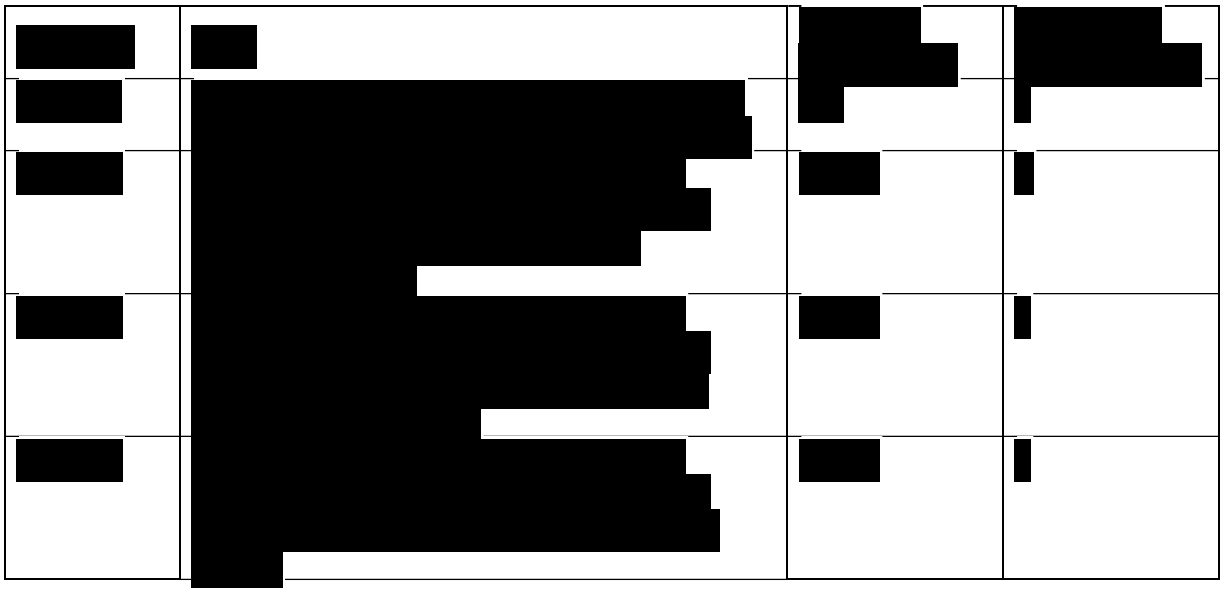
[redacted]

## 16.2 Data Listings

[redacted]

[redacted]



# 17.0 RECORD RETENTION

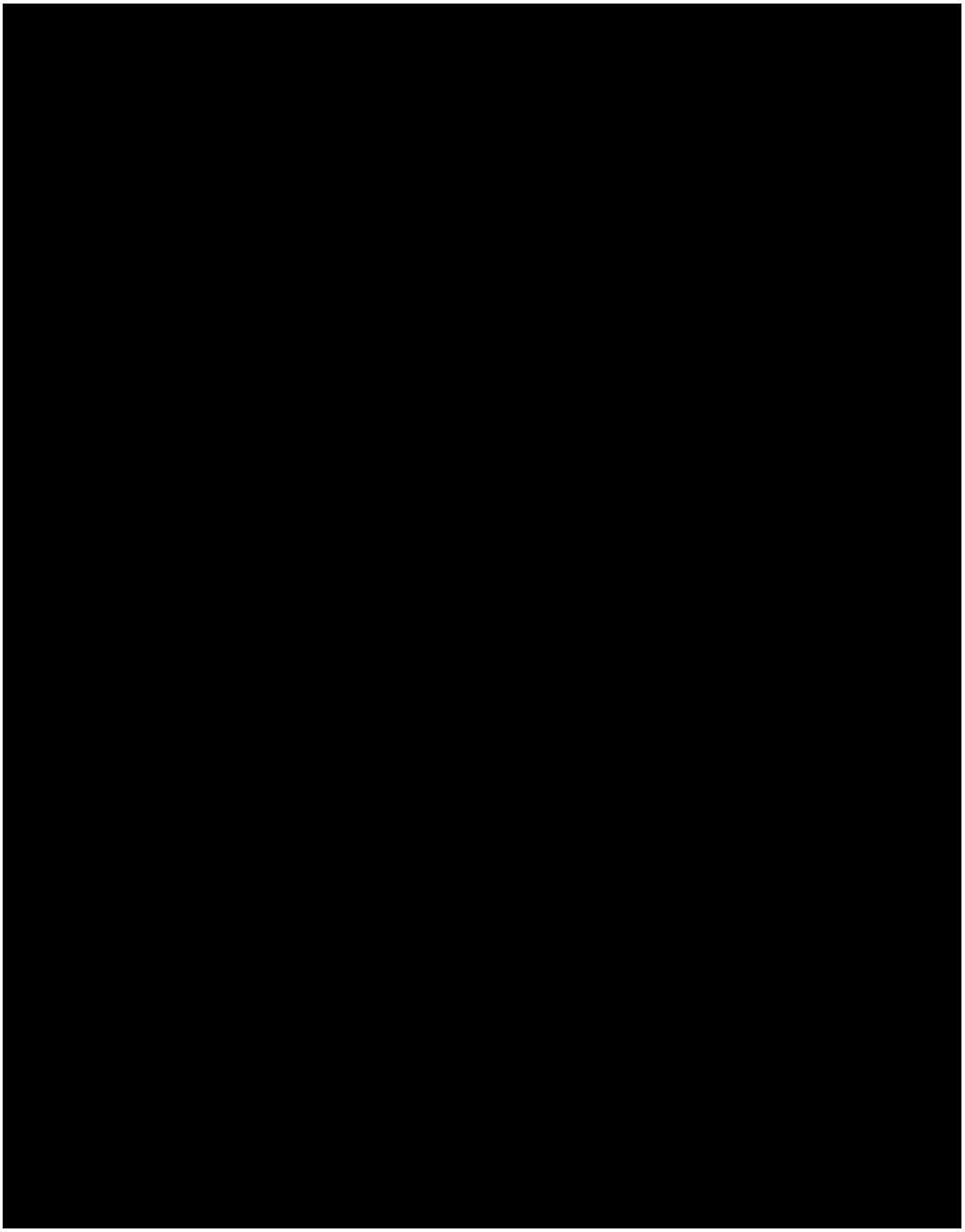
Records related to the activities listed in this plan will be retained according to AC SOP AD-005.

# 18.0 CHANGE HISTORY

| Version | Date | Description of Changes |
|---|---|---|
| 1.0 | Current version is final as of the last approval signature | Original Document |

# 19.0 APPENDICES

**Figure 1: Study Flow Chart**



[redacted]

**Table 6: Schedule of Events**

[redacted]

[redacted]

[redacted]

# SIGNATURES PAGE

| Date | Signed by |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |