A Randomized, Evaluator-Blinded, Parallel, Comparator-Controlled Study to Evaluate the Safety and Effectiveness of GAL1704 for Cheek Augmentation and Correction of Midface Contour Deficiencies

NCT Number: NCT03700047

14Dec2018

[redacted]

[redacted]

GALDERMA

Galderma Research and Development, LLC

Protocol Number: 43USV1704

Statistical Analysis Plan

Version 1.0

[redacted]

Advanced Clinical

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Version: *1.0*

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TABLES

[redacted]

1.0 PURPOSE

This SAP describes the methods to be used in the analysis of study data from clinical protocol 43USV1704 titled "A Randomized, Evaluator-Blinded, Parallel, Comparator-Controlled Study to Evaluate the Safety and Effectiveness of GAL1704 for Cheek Augmentation and the Correction of Midface Contour Deficiencies" in order to answer the study objective(s), and is based on version 3.0 of the study protocol, dated 28AUG2018.

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 database lock 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
AESI	Adverse Event of Special Interest
ATC-3	Anatomical Therapeutic Chemical 3th level
BE	Blinded Evaluator
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CDISC	Clinical Data Interchange Standards Consortium
CIPR	Central Independent Photographic Reviewer
CSR	Clinical Study Report
G	Gram
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early termination
eCTD	Electronic Common Technical Document
FST	Fitzpatrick Skin Type
[redacted]	[redacted]
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

Abbreviation	Description
[redacted]	[redacted]
NPS	Numeric Pain Scale
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TC	Telephone Call
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 demonstrate non-inferiority of GAL1704 versus a comparator-control in cheek augmentation by comparing change from baseline in the blinded evaluator (BE) live assessment of midface fullness at 12 weeks after the last injection, [redacted].

3.1.2 Secondary Effectiveness Objectives

[redacted]

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

[redacted]

3.1.3 Safety Objectives

The safety objectives of this study are:

i) To evaluate all adverse events (AEs) collected throughout the study.

ii) To evaluate pre-defined, injection related events (IREs) reported during the first 4 weeks after each treatment as recorded in the subject diary.

iii) To evaluate subject pain for each cheek individually – before (prior to application of anesthetic) and immediately following (before any post-injection procedures) each injection session using an [redacted] Numeric Pain Scale (NPS).

iv) To evaluate the following safety assessments, as assessed by a qualified staff member, according to pre-defined methods, at baseline and each subsequent on-site follow up visit:

[redacted]

3.1.4 Exploratory Objectives

[redacted]

[redacted]

3.2 Study Design and Study Procedures

This is a randomized, evaluator-blinded, parallel group, comparator-controlled, multi-center, US study to evaluate the effectiveness of GAL1704 for cheek augmentation and the correction of midface contour deficiencies.

3.3 Treatments and Assignment to Treatments

Subjects will be enrolled in two groups – Group A and Group B.

Group A: Approximately 210 subjects, over the age of 21, will be randomized in a 2:1 ratio, to receive treatment with either GAL1704 or Juvéderm Voluma® XC, respectively. Approximately 140 subjects will be treated with GAL1704 and 70 subjects will be treated with Juvéderm Voluma® XC. [redacted] sites will have a BE, blinded to the treatment provided to each subject, who will perform the blinded assessments.

Group B: An additional 60 subjects will be enrolled and treated with GAL1704 only. These subjects will be treated using a split face design, i.e., one cheek will be treated using a small blunt tip cannula and the other cheek will be treated using the co-packed needle. [redacted]

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[redacted]

[redacted]

he Treating Investigator will not be blinded to study treatments and will administer the treatments to each subject. Safety assessments will be performed by non-blinded personnel.

[redacted]

[redacted]

[redacted]

[redacted]

3.4 Determination of Sample Size

For sample size calculation of Group A, [redacted]

[redacted]

[redacted]

Accounting for approximately 12% drop-outs and non-evaluable subjects due to protocol deviations at Week 12, a total of approximately 210 subjects will be randomized in the study. It is expected that the number of randomized subjects will be similar across the study sites.

For sample size calculation of Group B, [redacted]

Accounting for approximately 10% drop-outs, 60 subjects will be needed.

[redacted]

Thus, a total of 270 subjects will be included in the study.

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.

Group A and Group B will be analyzed and presented separately. Data will be summarized by treatment group in Group A and by injection tool (Needle/Cannula) in Group B.

Confidence intervals will be two-sided and constructed at a confidence level of 95%.

Study days will be calculated relative to the date of first dose of study product. Day 1 will be the first day of study product administration in the study. 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.

[redacted]

4.1 Study Visits

[redacted]

4.2 Visit Windows

Study visits are expected to occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative study day of all dates will be presented. There will not be any windowing for unscheduled visits in the analysis. Unscheduled visits, if any, will be considered in determination of baseline.

5.0 ANALYSIS POPULATIONS

The Analysis Populations are defined separately for Group A and Group B as described below.

- **Safety Population:** Includes all subjects who were injected at least once. Subjects are analysed according to the treatment they actually received.

- **Intention-to-Treat (ITT) Population:** Includes all subjects who were randomized. Subjects are analysed according to the treatment they were randomized to.

- **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.

  Safety population will be the basis for all safety evaluations. When performing effectiveness analysis, the ITT population will be used. Primary effectiveness analysis will be repeated using the PP populations. Additional endpoints maybe explored in the PP population if deemed necessary.

6.0 SUBJECT DISPOSITION

Subject disposition will be summarized separately for Group A and Group B. 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.

Subject accountability will be summarized by visit with the following:

i) Number of subjects expected at each visit
ii) Number of subjects performed each visit
iii) Number of subjects missed at each visit
iv) Number of subject withdrawn at each visit

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. Number and percentage of subjects with each type of protocol deviation will be summarized by site for individual treatment group and overall, as appropriate, for the ITT population.
Depending on the seriousness of the deviation, subject might be excluded from the PP population, which shall be documented prior to database lock. [redacted]

[redacted]

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. The variables to be summarized are described below:

- Continuous variables
  - Age (years)
  - Body Mass Index (BMI) (kg/m2)

- Categorical variables
  - Sex (Female, Male)
  - Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)

Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Fitzpatrick Skin Types (FST) (I, II, III, IV, V, VI)

[redacted]

FST is a skin classification system that categorizes different skin colors, and their reactions to ultraviolet light. [redacted]

[redacted]

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, as appropriate, for the ITT population as given below:

i) Medical history for each body system including number of events, number of subjects (n) and percentage (%).
ii) Medical history occurring in >= 2% of subjects.
iii) Allergy history for each body system including number of events, number of subjects (n) and percentage (%).
iv) Cosmetic/Aesthetic Procedures and Implant History including number of procedures, number of subjects (n) and percentage (%).

Medical history, Allergy history, and Cosmetic/Aesthetic Procedures and Implant History information will be reported by treatment and subject in separate data listings.

9.0 EFFECTIVENESS VARIABLES

9.1 Primary Effectiveness Variable

Change from baseline in the blinded evaluator (BE) live assessment of midface fullness, for the right and left side of the face, at 12 weeks after the last injection, [redacted].

9.2 Secondary Effectiveness Variables

[redacted]

10.0 EFFECTIVENESS ANALYSIS

Group A and Group B will be analysed and presented separately.

The primary analysis will be repeated in the per protocol (PP) population.

10.1 Primary Effectiveness Analysis

Primary effectiveness analysis (Group A only)

[redacted]

a) Non-inferiority will be established if the upper limit of the CI is below the non-inferiority margin of 0.5 units.
b) Superiority will be declared if the upper limit is below 0.

This decision criteria is consistent with a gate-keeping strategy (testing for superiority following the test for non-inferiority) to maintain the overall type I error rate at 2.5%.

[redacted]

[redacted]

Group B effectiveness success criterion

[redacted] The CI will be used for assessing non-inferiority in the following way. Non-inferiority will be established if the upper limit of the CI is below the non-inferiority margin of 0.5 units.

[redacted]

10.2 Secondary Effectiveness Analysis

[redacted]

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[redacted]

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[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.

[redacted]

Impact of missing data on the primary analysis for Week 12 endpoints will be evaluated by performing sensitivity analysis based on the observed cases in the ITT population.

[redacted]

All other effectiveness endpoints will be evaluated based on the observed cases in ITT, i.e. no imputations will be done.

If the adverse event start date is missing, it will be assumed that the AE started on the day of the most recent treatment. Missing stop date for adverse event will not be imputed.

If the adverse event severity assessment is missing, the highest level of severity will be assumed. Missing relationships in adverse event will be imputed as related. AEs will be considered as serious if the assessment on whether the AE is serious or not is missing.

The observed cases in the Safety population will be used for all other safety analysis.

11.2 Pooling of Centers in Multi-Center Studies

Pooling of centers might be needed for subgroup analysis based on study site, if there are study sites with few subjects. For Group A, sites with less than or equal to three subjects will be pooled together and for Group B, sites with less than or equal to four subjects will be pooled together.

11.3 Multiple Comparisons/Multiplicity

Gate-keeping strategy [redacted] is used for adjustments for multiple comparisons or multiplicity.

[redacted]

11.4 Examination of Subgroups

Robustness of the results of the primary endpoint analysis will be investigated across the subgroups of subjects determined by factors according to the exploratory objectives [redacted]

To evaluate consistency of AEs across different subgroups, AEs will also be summarized by 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, and optional re-treatment separately for safety population.

Following parameters will be summarized for left and right side of the midface combined for extent of exposure in Group A:

- Total Volume Injected
- Type of Needle Used
- Injection Depth
- Injection Method

Following parameters will be summarized for left and right side of the midface, separate for the side treated with needle and the side treated with cannula, for extent of exposure in Group B:

- Total Volume Injected
- Injection Tool Used
- Cannula Brand
- Cannula Gauge
- Cannula Length
- Type of Needle
- Type of Cannula
- Injection Depth
- Injection Method

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

Following parameters will be summarized for treatment procedure:

- Procedural Anesthetics (No, Yes)
- Type of Anesthetics (Topical, Local Injection, Nerve Block)

- Injection Concomitant Procedures (None, Massage, Ice Pack, Other)

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

13.0 SAFETY ANALYSIS

Group A and Group B will be analysed and presented separately. Group A safety analysis will be performed with right and left side of the midface combined. Group B safety results will be summarized separately for the needle and cannula sides of the face (to compare the treatment tools).

The safety endpoints include:

- Evaluation of all adverse events (AEs) including Adverse Events of Special Interest (AESIs).

- Pre-defined, injection related events (IREs) reported during the first 4 weeks after treatment as recorded in the subject diary.

- Evaluation of subject pain for each cheek individually – before (prior to application of anesthetic) and immediately following (before any post-injection procedures) each injection session using an [redacted] Numeric Pain Scale (NPS).

[redacted]

[redacted]

[redacted]

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 treatment for subjects will be included in analysis. AEs occurring before, if any, will only be listed in subject data listings. Missing dates, severity, relationship, and seriousness will be imputed as described in section 11.1.

All AE endpoints will be summarized for Group A and Group B separately by treatment as follows:

i) Initial treatment; after their first treatment up until their optional retreatment, or end of study.
ii) Retreatment; after their optional retreatment up until end of study.

For AE analysis, Touch-up treatment will not be analyzed separately, thus initial treatment + touch-up will be counted as 1 treatment.

Apart from the summary of AEs table described below, all other AE tables will be presented by treatment as follows:

Group A – separate columns for each treatment group.

Group B – one column with AEs associated with side treated with needle, one column with AEs associated with side treated with cannula, and one total column including the total of the first two columns + AEs not associated with any side.

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 with at least one adverse events of special interest (AESI), and number of events (in total as well as serious AEs)
v) number of subjects who did not have an AE

Summary of AEs table will be presented by treatment for Group A.

For Group B, this summary table will be presented in one total column. In addition, there will be one row for AEs related to side treated with needle, one row for AEs related to side treated with cannula, and a row for AEs related but not to a specific treatment area.

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.

The number of subjects with AEs unrelated to both study product and injection procedure as well as the number of events will be summarized by SOC, PT, and severity.

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.

[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) using a table with related AEs by SOC, PT and severity.

[redacted]

Hypertrophic scarring/hyperpigmented scarring will be summarized by FST I-III, IV, and V-VI.

Incidences of visual disturbances are considered Adverse Events of Special Interest (AESIs) and include but are not limited to the following: loss of vision, blurry vision, double vision, pain in or around the eye, blind spot or shadow in the visual field, trouble moving eyes, etc.
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, serious AEs, and AESIs. Adverse events with late onset (onset >21 days) will be provided in a listing.

13.2 Pre-defined, expected, post-treatment events

[redacted]

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, [redacted] will be presented by treatment, type of event and maximum severity. Number of days with the event will be summarized by treatment [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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13.10 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.

[redacted]

[redacted]

13.12 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 3rd level (ATC-3) and preferred name for concomitant medications. This table will include only those medications that are taken by >2% of the subjects. If the 3rd level term is not available, the next available level (e.g., ATC-2) will be used. A subject will only be counted once within each ATC-3 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.

[redacted]

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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.

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).

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

Galderma Research and Development, LLC — Page x of y
Protocol: 43USCH1702 — Run Date: DDMMMYY HH:MM
Clinical Study Report

Listing 16.2_x (or Table 14.x_x)
<Title>
<Population>

Col 1 Col 2 Col 3 Etc.

<Any footnotes>

File Name: <pathname for SAS 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.

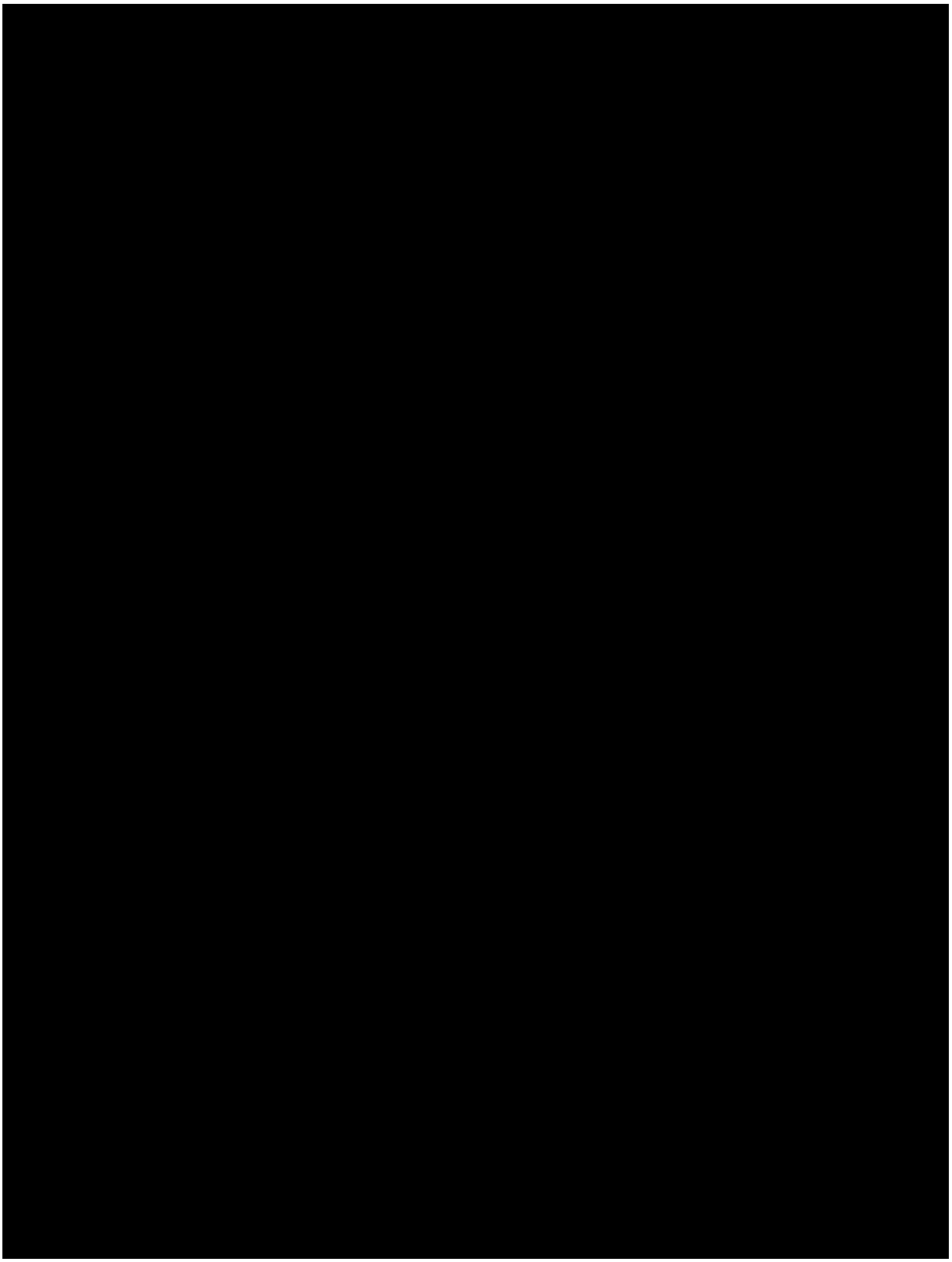
16.0 RECORD RETENTION

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

[redacted]

[redacted]

19.0 APPENDICES



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