Statistical Analysis Plan

NCT Number: NCT05687916

Title: A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy Without Cataplexy (Narcolepsy Type 2)

Study Number: TAK-861-2002

Document Version and Date: Amendment 2.0, 06 December 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-861-2002

Study Title:

A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy Without Cataplexy (Narcolepsy Type 2)

Phase: 2

Version: Amendment 2

Date: 06 December 2023

Prepared by: [redacted]

Based on:

Protocol Version: Initial

Protocol Date: 13 Sep 2022

REVISION HISTORY

Version	Date	Primary Rationale for Revision
Initial	04 Jan 2023	Not Applicable
Amendment 1	24 Jul 2023	[redacted]
Amendment 2	15 Nov 2023	[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF FIGURES

ABBREVIATIONS

[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	data monitoring committee
DNS	disturbed nighttime sleep
ECG	electrocardiogram
e-diary	electronic diary
EDS	excessive daytime sleepiness
[redacted]	[redacted]
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full Analysis Set
[redacted]	[redacted]
[redacted]	[redacted]
GEE	generalized estimating equations
HR	heart rate
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
LS	Least square
LTE	long-term extension
MAMS	multi-arm multi-stage
[redacted]	[redacted]
MCT	meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MWT	Maintenance of Wakefulness Test

[redacted]	[redacted]
[redacted]	[redacted]
NT1	narcolepsy type 1
NT2	narcolepsy type 2
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PSG	polysomnography
[redacted]	[redacted]
QD	once daily
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
SAE	serious adverse event
SD	standard deviation
SE	standard error
[redacted]	[redacted]
SL	Sleep latency
SOC	System Organ Class
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
[redacted]	[redacted]
WHO drug	World Health Organization Drug Dictionary

Note: text in italics represents language copied directly from the protocol.

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

- *To assess the effect of TAK-861 on EDS as measured by sleep latency from the MWT.*

1.1.2 Secondary Objectives

- *To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score.*
- *To evaluate the safety and tolerability of TAK-861.*

1.1.3 Exploratory/Additional Objectives

[redacted]

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

- *Change from baseline to Week 8 in mean sleep latency from the MWT*

1.2.2 Secondary Endpoints

- *Change from baseline to Week 8 in ESS total score*
- *Occurrence of at least 1 treatment-emergent adverse event (TEAE).*

1.2.3 Exploratory/Additional Endpoints

[redacted]

[redacted]

1.3 [redacted]

1.3.1 [redacted]

[redacted]

Table 1.a [redacted]

[redacted]

Table 1.a [redacted]

[redacted]

1.3.2 [redacted]

[redacted]

Table 1.b [redacted]

[redacted]

2.0 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, 8-week parallel group study to evaluate the efficacy, safety, and tolerability of 2 oral dose regimens of TAK-861. Approximately 60 (male and female) participants with NT2, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any of 3 treatment arms: 2 TAK-861 dose regimens or matching placebo.

[redacted]*. Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 8 weeks.*

Participants who have provided informed consent will complete a screening period of up to 45 days to washout any NT2 medication (if applicable). Participants will be asked to complete an eDiary, starting from the initial screening visit, no later than [redacted].

[redacted]

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

After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). Participants who enroll in the LTE study will not have follow-up visits captured under this study protocol.

[redacted]

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

3.1.1 Primary Endpoint

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the mean sleep latency (minutes) from the 4 sessions of a 40-minute MWT. The statistical null hypothesis is that the mean change from baseline to Week 8 in the mean sleep latency for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 in the mean sleep latency for the placebo treatment group.

3.2 Secondary Endpoints

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the total ESS score. The statistical null hypothesis is that the mean change from baseline to Week 8 in the total ESS score for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 for the placebo treatment group.

3.3 Statistical Decision Rules

Not applicable.

3.4 [redacted]

[redacted]

Figure 3.a

4.0

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety set will consist of all participants who received at least 1 dose of study drug. This analysis set will be used for demographic, baseline characteristic, and safety summaries.

5.2 Full Analysis Set

The full analysis set will consist of all participants who were randomized and received at least 1 dose of study drug and have at least one postdose efficacy measurement. Efficacy measurements only include MWT and ESS. *The full analysis set will be used for summaries of efficacy* and applicable exploratory *endpoints.*

5.3 [redacted]

[redacted]

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All p-values reported will be 2-sided and reported to 3 decimal places.

All continuous variables will be summarized with descriptive statistics (N, mean, median, standard deviation (SD), minimum, and maximum) unless stated otherwise. The denominator for any percentages will be based on the number of participants who provided nonmissing responses to the categorical variable.

6.1.1 Handling of Treatment Misallocations

For efficacy, treatment misallocations will be analyzed as randomized. For safety, treatment allocations will be analyzed as treated.

6.1.2 Analysis Approach for Continuous Variables

[redacted]

[redacted]

6.1.3 Analysis Approach for Binary Variables

The analysis approach for binary variables will be described in the specific sections.

6.2 Disposition of Subjects

The number and percentage of participants in the following categories will be summarized by treatment group, TAK-861 overall, and total:

- Randomized
- Randomized and not treated (including reasons not treated)
- Randomized and treated
- Prematurely discontinued from study treatment
- Primary reason off study treatment
- Prematurely discontinued from the study
- Primary reason off study

The number and percentage of participants randomized in each [redacted] site will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants in each analysis set will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants with significant protocol deviations will be summarized by treatment group, TAK-861 overall, and total.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

A summary of demographics (age, gender, ethnicity, and race) for screen failures and the primary reason for failure will be provided.

Demographics (age, gender, ethnicity, and race) will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize data for continuous variables and for categorical variables the number and percentage of participants within each category will be summarized.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions that ended before signing of the informed consent. Concurrent medical conditions are those significant conditions that are ongoing at the signing of the informed consent. Medical history and concurrent medical conditions will be

coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 25 or higher) coding system.

Medical history and concurrent medical conditions will be summarized for each treatment group, TAK-861 overall, and total using the Safety Set. The number and percentage of participants with at least one event in each MedDRA system organ class (SOC) and preferred term (PT) will be summarized. A participant with multiple occurrences of medical history or concurrent medical conditions within a SOC or PT will be counted only once in that SOC or PT.

6.3.3 Baseline Characteristics

Baseline characteristics (alcohol, caffeine, and tobacco use at time of informed consent, years since diagnosis (relative to informed consent), age at diagnosis, years since symptom onset (relative to informed consent), age at symptom onset, prior use of narcolepsy medications (requiring washout), mean sleep latency from the MWT, ESS total score, [redacted] will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize continuous variables and the number and percentage of participants within each category will be summarized for categorical variables.

6.4 Medication History and Concomitant Medications

All medications will be coded using World Health Organization Drug Dictionary (WHO Drug) (WHO Drug Global B3 March 2022 or higher).

6.4.1 Prior Medications

Prior medications are defined as any medications that stopped prior to the first dose of study drug. Prior medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class. Prior medications for narcolepsy (requiring washout) will also be summarized by standardized medication name.

6.4.2 Concomitant Medications

Concomitant medications are defined as any medications that started prior to the first dose of study drug and are ongoing at the time of the first dose or started after the first dose of study drug, but before the date of last TAK-861 dose. Concomitant medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class.

6.5 Efficacy Analysis

6.5.1 [redacted]

[redacted]

6.5.1.1 [redacted]

[redacted]

6.5.1.2 [redacted]

[redacted]

[redacted]

[redacted]

6.5.1.3 [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

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6.5.1.4 [redacted]

[redacted]

6.5.1.5 [redacted]

[redacted]

6.5.1.6 [redacted]

[redacted]

[redacted]

6.5.2 [redacted]

[redacted]

6.5.2.1 [redacted]

[redacted]

6.5.2.2 [redacted]

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

[redacted]

[redacted]

6.5.2.3 [redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

6.5.2.4 [redacted]

[redacted]

6.5.2.5 [redacted]

[redacted]

6.5.3 Subgroup Analyses

Not applicable.

6.6 Safety Analysis

[redacted] will be provided in a programming specifications document.

6.6.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA (v25.0 or higher). A treatment-emergent adverse event (TEAE) is defined as an AE whose date/time of onset occurs on or after the first dose of study drug.

Treatment-Emergent Adverse Events (TEAE) summary tables will include the number and percentage of participants experiencing at least one TEAE by SOC and PT and will be tabulated by treatment. The following is a list of TEAE summary tables to be generated:

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events by Preferred Term
- Most Frequent Treatment-Emergent Adverse Events by Preferred Term (at least 2 in any treatment arm)
- Most Frequent (> 5% participants in any treatment) Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

For the subset of participants with at least one urinary symptom, the frequency of participants with ≥ 1 instance of increased urinary frequency, and a summary of the number of times participants normally urinate during night-time hours prior to start of treatment and at the time of the urinary events will be generated.

6.6.2 Adverse Events of Special Interest

The adverse events of special interest (AESI) are noted below:

- BP and HR increases
- Insomnia
- Bladder events

A separate summary of AESIs will be generated.

6.6.3 Other Safety Analysis

6.6.3.1 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. A list of all the clinical laboratory evaluations can be found in Protocol Section 10.2.

Descriptive statistics of clinical laboratory variables (chemistry and hematology) will be summarized for baseline and postdose values, as well as change from baseline to postdose values by study visit and treatment group and TAK-861 overall. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

For each lab test parameter,

6.6.3.2 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), heart rate, respiratory rate, body temperature, and weight. Only the scheduled measurements will be included in summary tables or statistical analysis of VS measurements.

Respiratory rate, weight and temperature will be summarized with descriptive statistics including the change from baseline at each visit by treatment group and TAK-861 overall. For respiratory rate and temperature, only summarize for baseline, week 2 (day 14), week 4 (day 28) , week 6 (day 42), week 8 (day 56).For weight, only summarize for baseline, week 4 (day 28), week 8 (day 56). Baseline is the last non-missing measurement prior to the first dose.

[redacted]

[redacted]

6.6.3.3 [redacted]

[redacted]

Table 6.i. [redacted]

[redacted]

Table 6.i. [redacted]

[redacted]

6.6.3.4 ECG

The continuous ECG parameters (heart rate, PR interval, QRS interval, QT interval, QT interval with Bazett correction method (QTcB) and QT interval with Fridericia correction method (QTcF) at each visit, and the change from baseline will be summarized with descriptive statistics by treatment group and TAK-861 overall. Only the ECGs collected at the scheduled visits will be included in the summary.

The ECG interpretation by the investigator (Within Normal Limits; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant, Not Evaluable) will be summarized at each visit by treatment group and TAK-861 overall.

[redacted]

6.6.3.5 C-SSRS

The number and percentage of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) [redacted] will be summarized by treatment group, and TAK-861 overall.

6.6.4 Extent of Exposure and Compliance

The summary of study drug exposure and compliance will be based on the Safety Set. The treatment duration is defined as (date of last dose – date of first dose +1). Treatment duration (days) will be summarized using descriptive statistics for each treatment group and TAK-861 overall.

Table 6.ii below describes the bottle types dispensed assuming 32 tablets per bottle:

Table 6.ii. Bottle Types Dispensed for Each Treatment Group

Treatment Group	[redacted]		[redacted]
	Bottle 1	Bottle 2	Bottle
Placebo	Placebo	Placebo	Placebo
2 mg twice daily	2 mg	Placebo	2 mg
2 mg followed by 5 mg	2 mg	Placebo	5 mg

TAK-861 bottle compliance will be calculated for each bottle type:

$$\frac{(\text{number of tablets dispensed from the bottle type} - \text{number of tablets returned from the bottle type})}{\text{Scheduled number of tablets asscociated with that bottle type} * (\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

For example, in the 2 mg twice daily group, the scheduled number of tablets associated with 2 mg bottle type is 2.

For active treatment groups, only the active bottle types are counted.

Placebo bottle compliance will be calculated as:

$$\frac{(\text{total number of tablets dispensed} - \text{total number of tablets returned})}{3 * (\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

The overall compliance for active treatment groups is the average of the compliance for the active bottle types.

The percent compliance for each bottle type and overall will be summarized with descriptive statistics by treatment group, and TAK-861 overall. In addition, the number and percentage of participants in the following compliance categories will be summarized: <70%, 70 to 100%, and >100% by treatment group.

6.7 [redacted] Biomarker Analyses

6.7.1 [redacted]

[redacted]

Table 6.iii. [redacted]

[redacted]

[redacted]

[redacted]

6.7.2 [redacted]

[redacted]

6.7.3 Biomarker Analysis

Not applicable.

6.8 [redacted]

6.8.1 [redacted]

[redacted]

6.8.1.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.8.1.2 [redacted]

[redacted]

[redacted]

6.8.1.3 [redacted]

[redacted]

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[redacted]

6.8.1.4 [redacted]

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6.8.1.5 [redacted]

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[redacted]

[redacted]

6.8.1.6 [redacted]

[redacted]

[redacted]

6.8.2 [redacted]

[redacted]

6.9 Other Analyses

6.9.1 [redacted]

[redacted]

6.9.1.1 [redacted]

[redacted]

[redacted]

[redacted]

6.9.1.2 [redacted]

[redacted]

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6.9.2 [redacted]

[redacted]

[redacted]

6.9.3 [redacted]

[redacted]

Table 6.iv [redacted]

[redacted]

6.9.4 Narcolepsy Symptoms (eDiary)

Weekly episodes for the following narcolepsy symptoms will be derived from the eDiary collection at baseline, Week 2, Week 4, Week 6, Week 8, and the 7-day post last dose follow-up visit:

- [redacted]

- [redacted]
- [redacted]
- [redacted]
- Disturbing and frightening dreams/nightmares
- Dreaming a lot or all night
- Problems falling asleep
- Good sleep quality (response of very good or fairly good)
- Number of naps

For number of naps, weekly episodes (WE) at baseline will be based on the number of episodes averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

$$WE = \left(\frac{number\ of\ episodes\ over\ a\ 2\ \text{week period}}{number\ of\ non-missing\ diary\ days\ in\ the\ 2\ week\ period}\right) * 7$$

Weekly episodes for number of naps in the 7-day post last dose follow-up visit is calculated as follows:

$$WE = \left(\frac{number\ of\ episodes\ over\ the\ follow-up\ \text{period}}{number\ of\ non-missing\ diary\ days\ in\ the follow-up\ period}\right) * 7$$

For all other endpoints, weekly episodes (WE) at baseline will be based on the number of episodes as averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

$$WE = \left(\frac{number\ of\ nights\ with\ an\ episodes\ over\ a\ 2\ \text{week period}}{number\ of\ non-missing\ diary\ days\ in\ the\ 2\ week\ period}\right) * 7$$

Weekly episodes for all other endpoints for the 7-day post last dose follow-up visit is calculated as follows:

$$WE = \left(\frac{number\ of\ nights\ with\ an\ episode\ over\ the\ follow-up\ \text{period}}{number\ of\ non-missing\ diary\ days\ in\ the\ follow-up\ period}\right) * 7$$

If a diary for a given day reports ≥ 0 episodes, the day will be counted as non-missing diary day. Otherwise, the day will be counted as a missing diary day for the symptom.

The diary compliance for narcolepsy symptoms will be summarized for each 2-week period. The number and percentage of participants with 0 days, 1 to 6 days, and >= 7 days with diary collection for narcolepsy symptoms will be summarized at baseline, week 2, week 4, week 6, and week 8.

The number of naps and weekly episodes of each narcolepsy symptom at each visit, change from baseline, and percent change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall.

Box plots of the number of naps and weekly episodes of each narcolepsy symptom by visit and treatment group will be generated.

The number of naps will be analyzed with a GEE model using a log-link function featuring a negative binomial distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction, and will be adjusted for baseline number of naps, age, and prior use of narcolepsy medications. An unstructured variance-covariance structure will be used initially in these models. If there are convergence issues with the model, an exchangeable variance-covariance structure will be used, followed by an independent structure. If lack-of-convergence still exists, the analysis will be done for Week 4 and Week 8 separately. The estimated incidence rate of weekly number of naps for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly number of naps (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and two-sided p-values.
The estimated weekly number of naps incidence rate ratio and the associated 95% CI of all TAK-861 treatment groups relative to placebo will be presented in forest plots, with one plot per visit (Week 2, Week 4, Week 6, and Week 8).

6.10 [redacted]

[redacted]

7.0 REFERENCES

[redacted]

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

- Updated the definition of full analysis set to include participants with at least one postdose efficacy measurement.

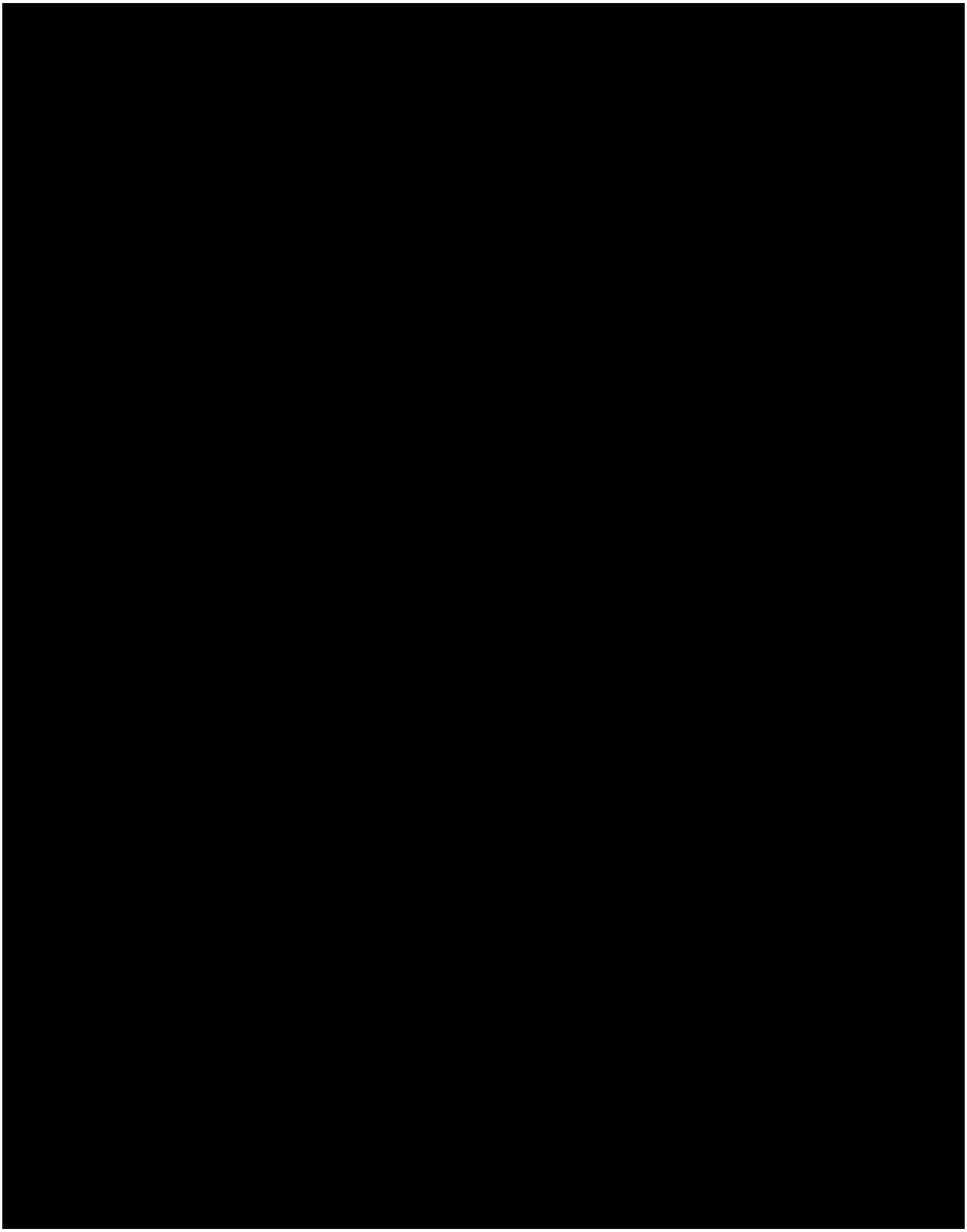
[redacted]

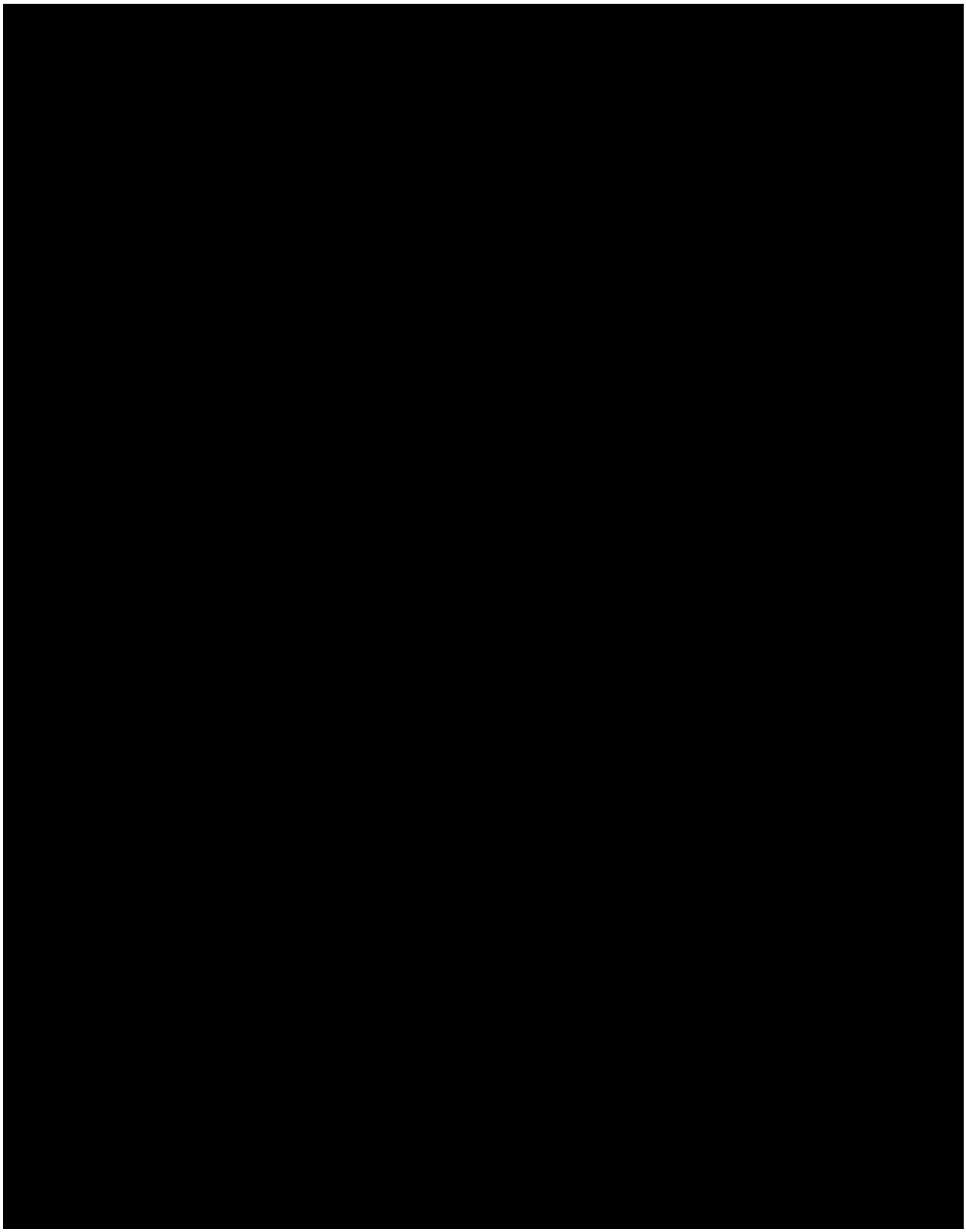
[redacted]

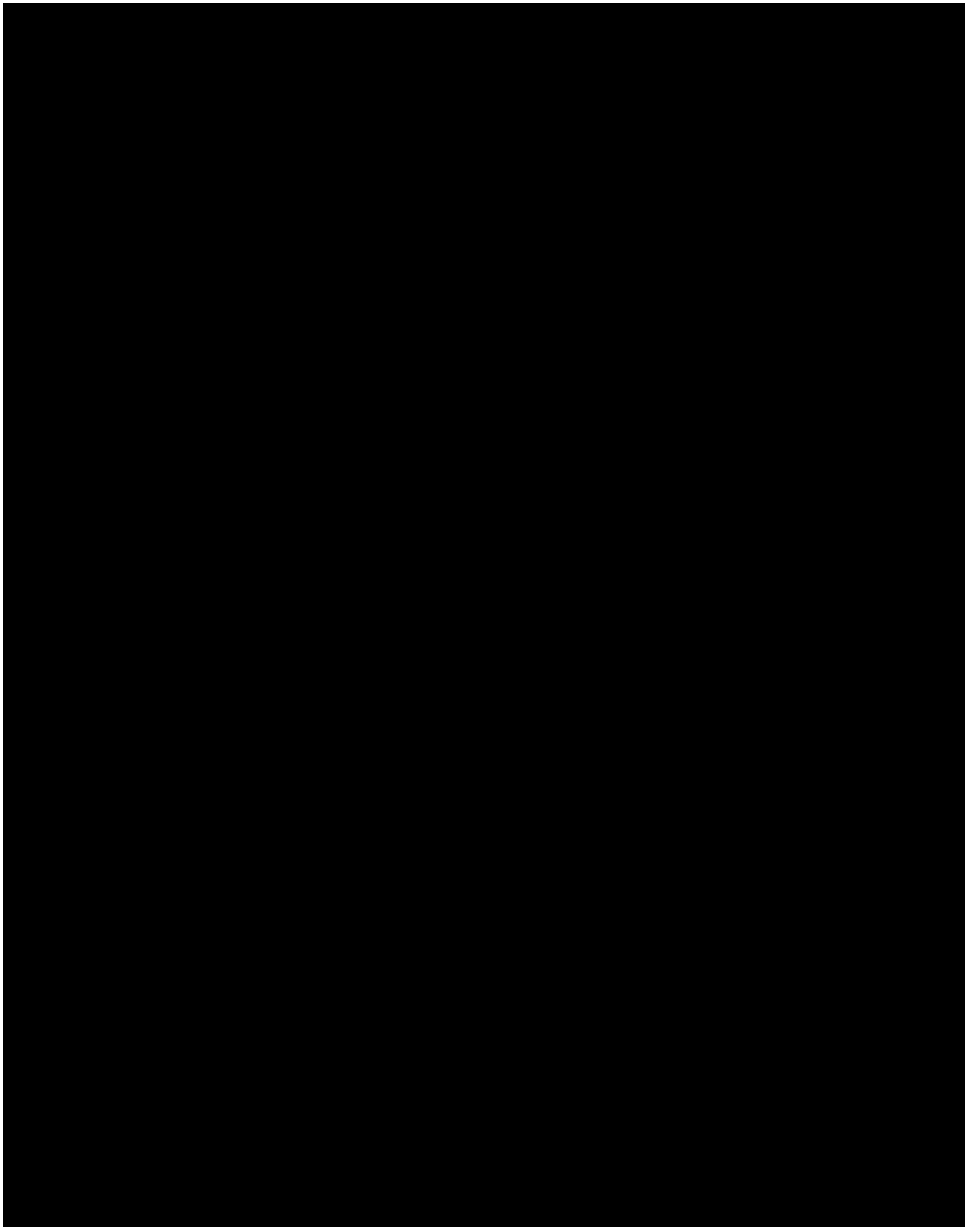
9.0 APPENDIX

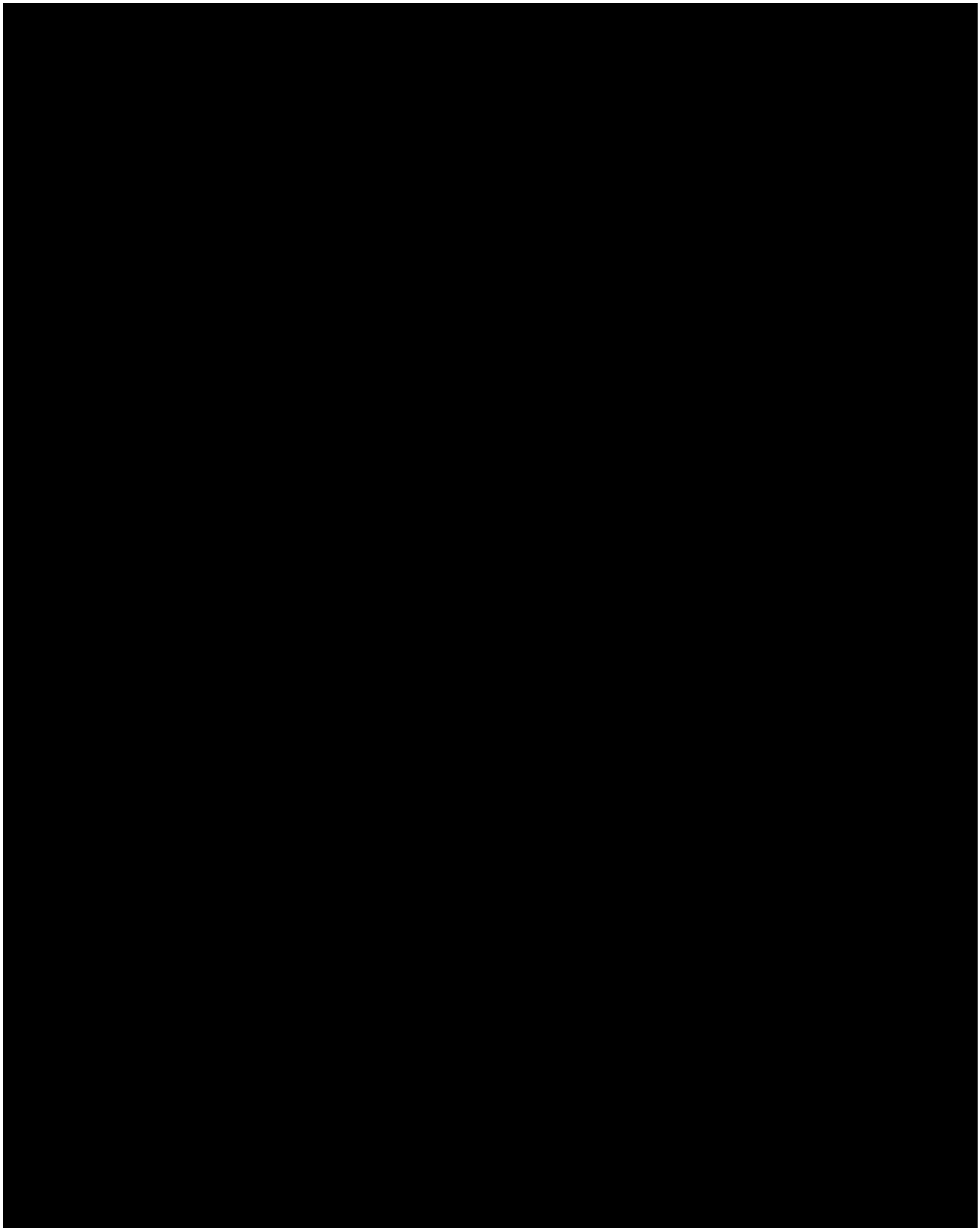
9.1 Changes From the Previous Version of the SAP

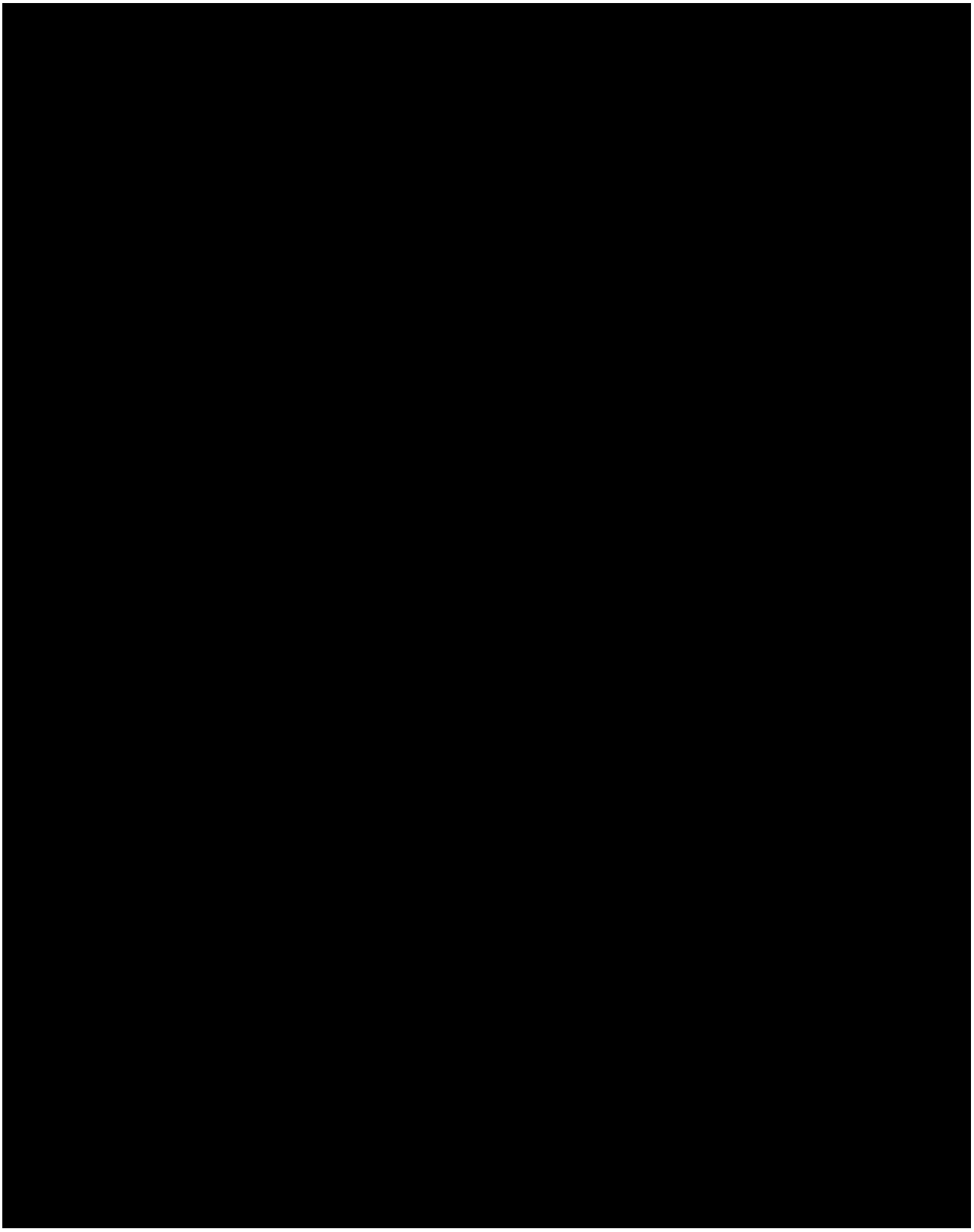
[redacted]











9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Refer to programming specifications.

9.2.2 Definition of Baseline

The definition of baseline is addressed in the specific section of the SAP.

9.2.3 Definition of Visit Windows

Refer to programming specifications.

Signature Page for 16-1-9-1 Statistical Analysis Plan Amendment 2 2023-12-08
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Approval	[redacted] Statistics 13-Dec-2023 21:36:57 GMT+0000

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