Statistical Analysis Plan

NCT Number: NCT05687903

Title: A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

Study Number: TAK-861-2001

Document Version and Date: Amendment 3.0, 11 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-861-2001

Study Title:

A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

Phase: 2

Version: Amendment 3

Date:11 December 2023

Prepared by: [redacted]

Based on:

Protocol Version: Initial

Protocol Date: 17 Aug 2022

REVISION HISTORY

Version	Date	Primary Rationale for Revision
Initial	29 Nov 2022	Not Applicable
Amendment 1	24 Jul 2023	[redacted]
Amendment 2	August 28 2023	[redacted]
Amendment 3	December 11 2023	[redacted]

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT 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
CPAP continuous positive airway pressure
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]
[redacted]	[redacted]
[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]
WCR	weekly cataplexy rate

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

1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

- *To assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by sleep latency from the Maintenance of Wakefulness Test (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 assess the effect of TAK-861 on cataplexy as assessed by the weekly cataplexy rate (WCR).*
- *To evaluate the safety and tolerability of TAK-861.*

1.1.3 Exploratory/Additional Objectives

[redacted]

1.2 Endpoints

1.2.1 Primary Endpoint

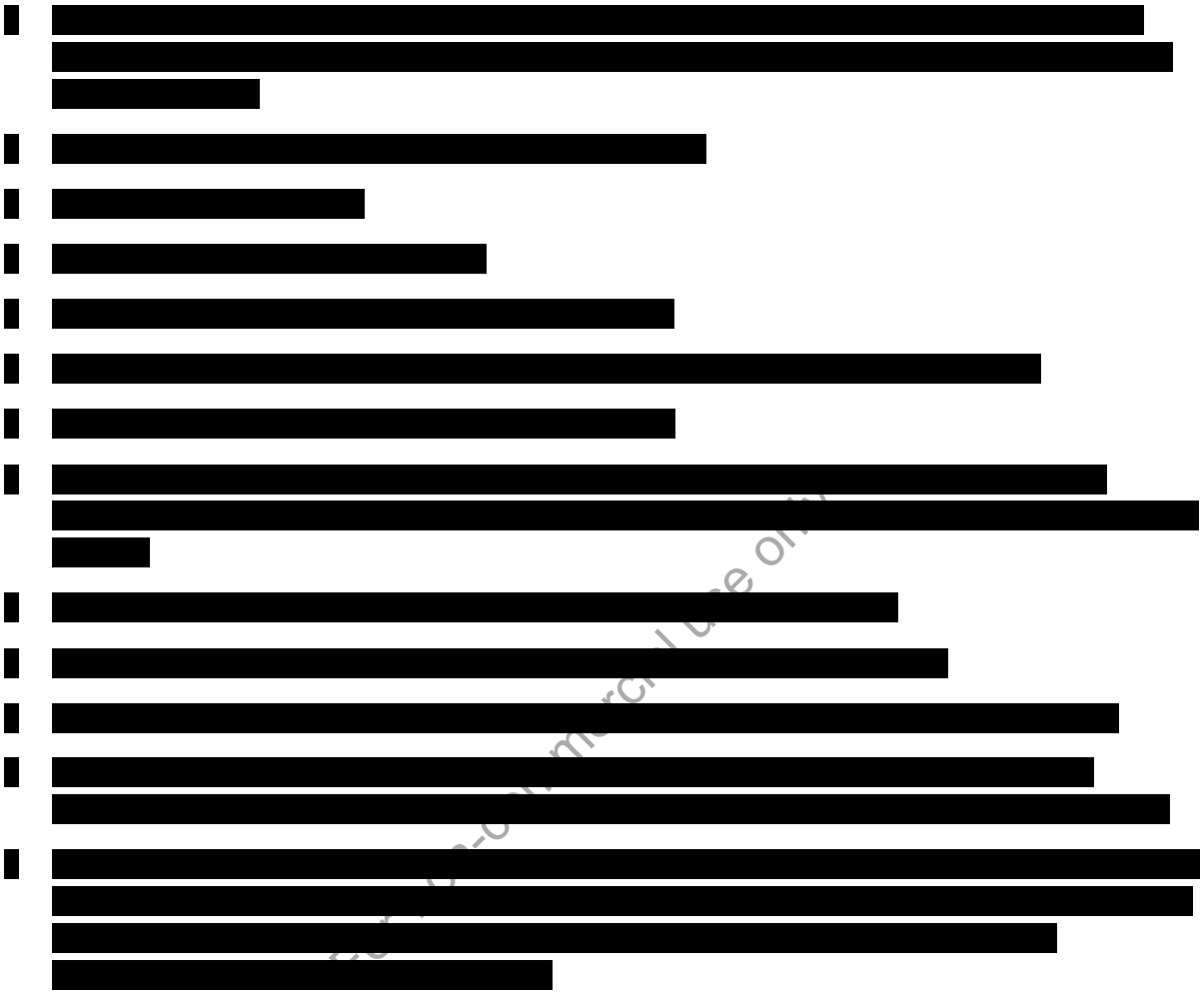
- *Change from baseline to Week 8 in mean sleep latency from the MWT*

1.2.2 Secondary Endpoints

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

1.2.3 Exploratory/Additional Endpoints

[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 4 oral dose regimens of TAK-861.

Approximately 100 (male and female) participants with NT1, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any 1 of 5 treatment arms: 3 TAK-861 twice daily dose regimens, 1 TAK-861 QD dose regimen, 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 or 12 weeks. (If the participant wishes to enroll in the long-term extension [LTE] study but the LTE study has not started at the participant's site when the participant completes the Week 8 visit of the current study, the participant will be allowed to continue in the current study for an additional 4 weeks; see below.)*

Participants who have provided informed consent will complete a screening period of up to 50 days to washout any NT1 medication (if applicable). Participants will be asked to complete

an e-diary, starting from the initial screening visit, no later than [redacted]. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least [redacted] day period from [redacted] and have ≥4 partial and/or complete episodes of cataplexy/week (averaged over [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 in this study.

If a participant plans to enroll in the LTE study but the LTE study is not open for enrollment at the participant's site when the participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment (continuing the same treatment regimen as the previous 8 weeks). This is to avoid a treatment gap for participants willing to roll over from this study to the LTE study.

[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.

TAK-861 is superior to placebo as measured by the WCR at Week 8. The statistical null hypothesis is that the incidence rate ratio (TAK-861 to placebo) of WCR at Week 8 is equal to 1.

3.3 Statistical Decision Rules

Not applicable.

3.4 [redacted]

[redacted]

[redacted]

Figure 1 [redacted]

4.0 [redacted]

[redacted]

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 include cataplexy, 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 non-missing 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]

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
- Continuing to Optional 4-Week Extension
- Continuing to the Long-Term Extension 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, human leukocyte antigen (HLA) status, 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], weekly cataplexy rate, [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 Primary Endpoint Analysis

6.5.1.1 [redacted]

[redacted]

6.5.1.2 [redacted]

[redacted]

[redacted]

[redacted]

6.5.1.3 [redacted]

[redacted]

[redacted]

6.5.2 Secondary Endpoints Analysis

6.5.2.1 [redacted]

[redacted]

6.5.2.2 [redacted]

6.5.2.2.1 [redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

6.5.2.2.2 [redacted]

[redacted]

6.5.2.3 [redacted]

[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.

[redacted]

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.

SBP, DBP and heart rate collected on Day 1, Week 4, and Week 8 will be summarized with descriptive statistics including the pre-dose value, postdose visit, [redacted] by treatment group and TAK-861 overall. [redacted]

[redacted]

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

Weight will be summarized with descriptive statistics at baseline, Week 4 and Week 8, including the change from baseline at each visit, by treatment group and TAK-861 overall. Baseline is the last non-missing measurement prior to the first dose.

[redacted]

6.6.3.3 [redacted]

[redacted]

[redacted]

[redacted]

Table 6.i. [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [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	Bottle 1	[redacted] Bottle 2	[redacted] Bottle
Placebo	Placebo	Placebo	Placebo
0.5 mg twice daily	0.5 mg	Placebo	0.5 mg
2 mg twice daily	2 mg	Placebo	2 mg
2 mg followed by 5 mg	2 mg	Placebo	5 mg
7 mg QD	2 mg	5 mg	Placebo

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 the 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]

[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]

[redacted]

6.8.1.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

6.8.1.2 [redacted]

[redacted]

[redacted]

[redacted]

6.8.1.3 [redacted]

[redacted]

[redacted]

[redacted]

6.8.1.4 [redacted]

[redacted]

[redacted]

6.8.1.5 [redacted]

[redacted]

6.8.1.6 [redacted]

[redacted]

[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]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.9.2 [redacted]

[redacted]

6.9.3 [redacted]

[redacted]

Table 6.iv [redacted]

[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 averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

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

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

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

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 featuring a negative binomial distribution similar to WCR.

6.10 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.11 Data Monitoring Committee/[redacted]

[redacted]

An external data monitoring committee (DMC) will review the safety and tolerability data on a quarterly basis, throughout the study. A DMC charter will provide full guidance on the function and practices to be followed by the DMC.

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]

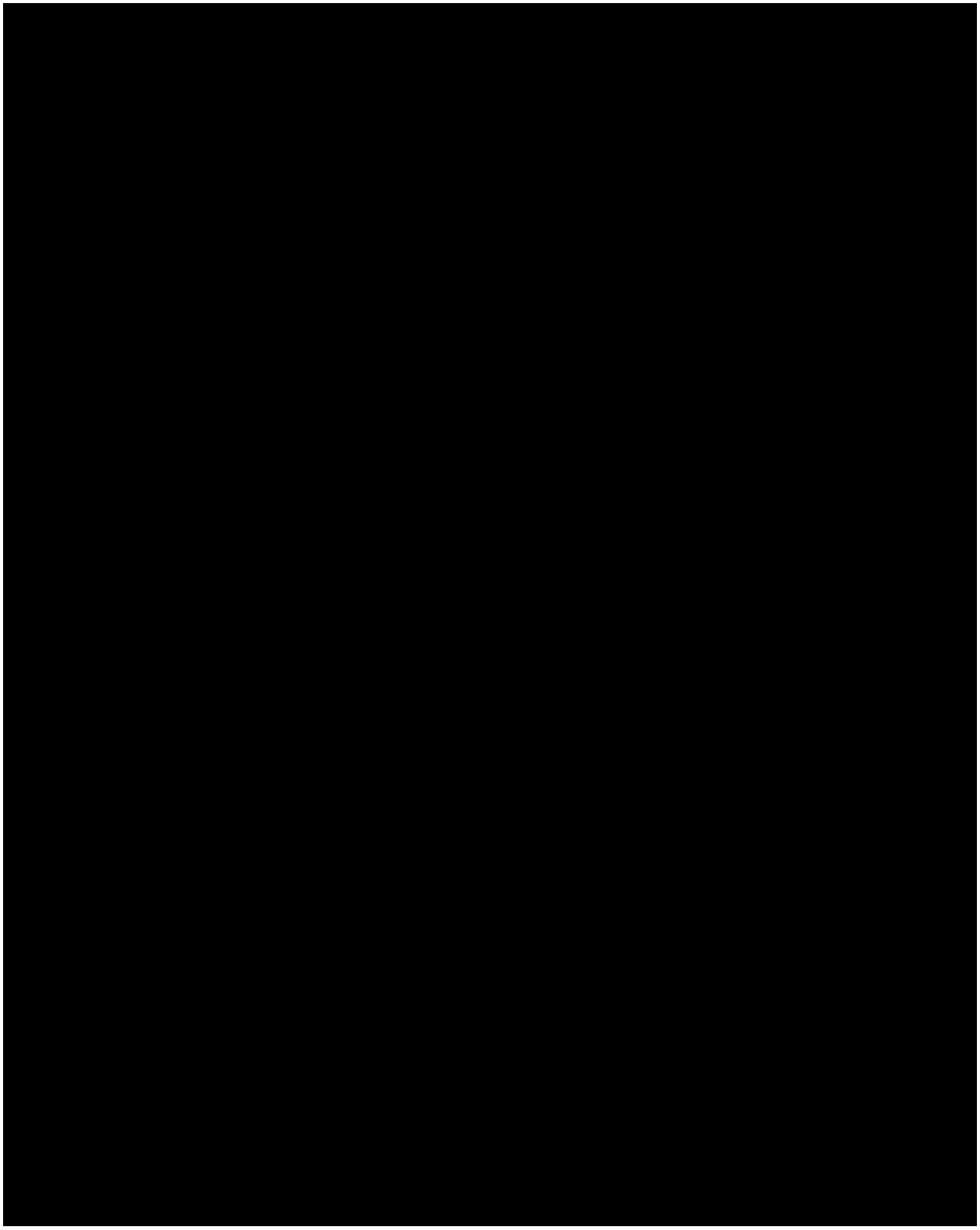
[redacted]

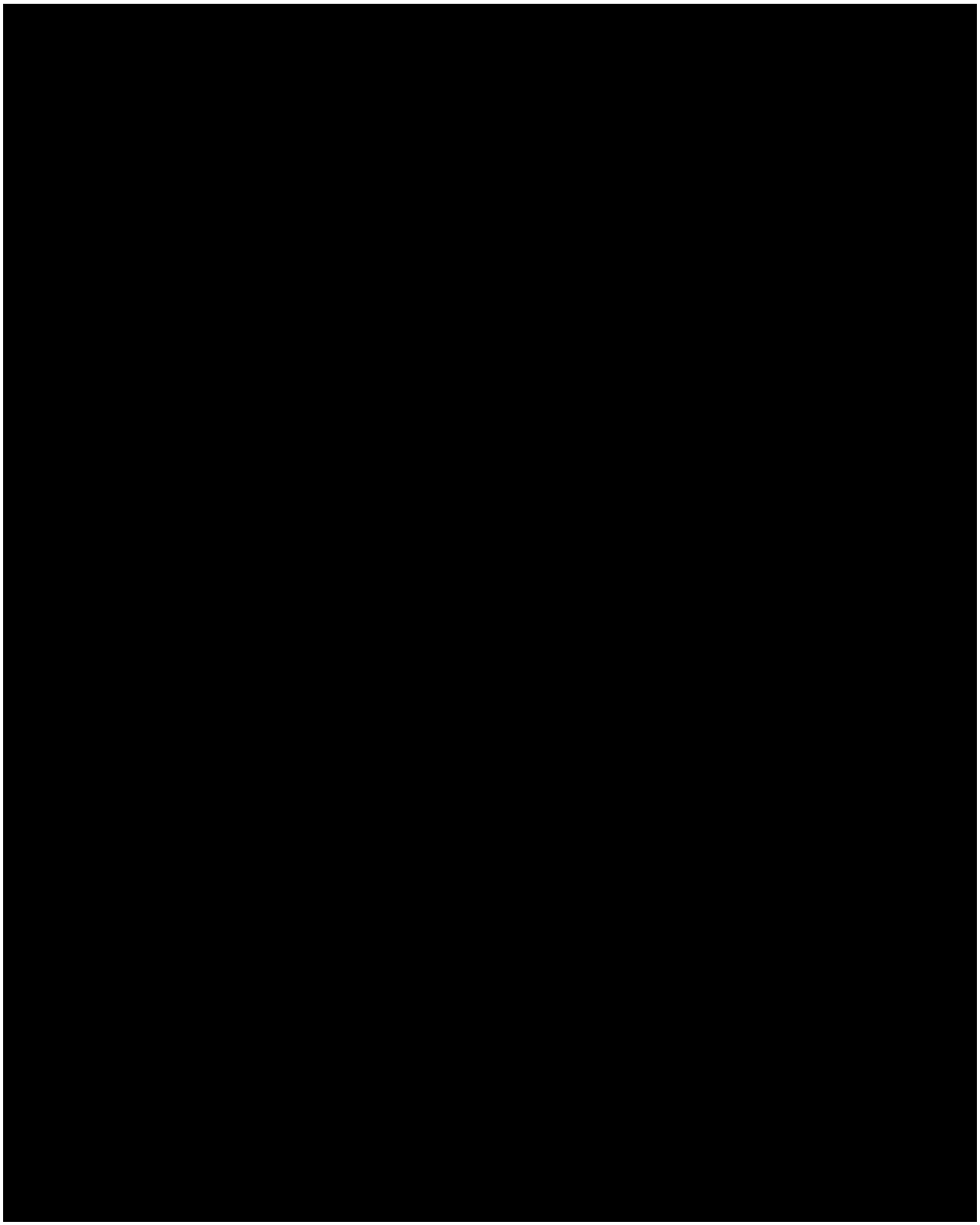
9.0 APPENDIX

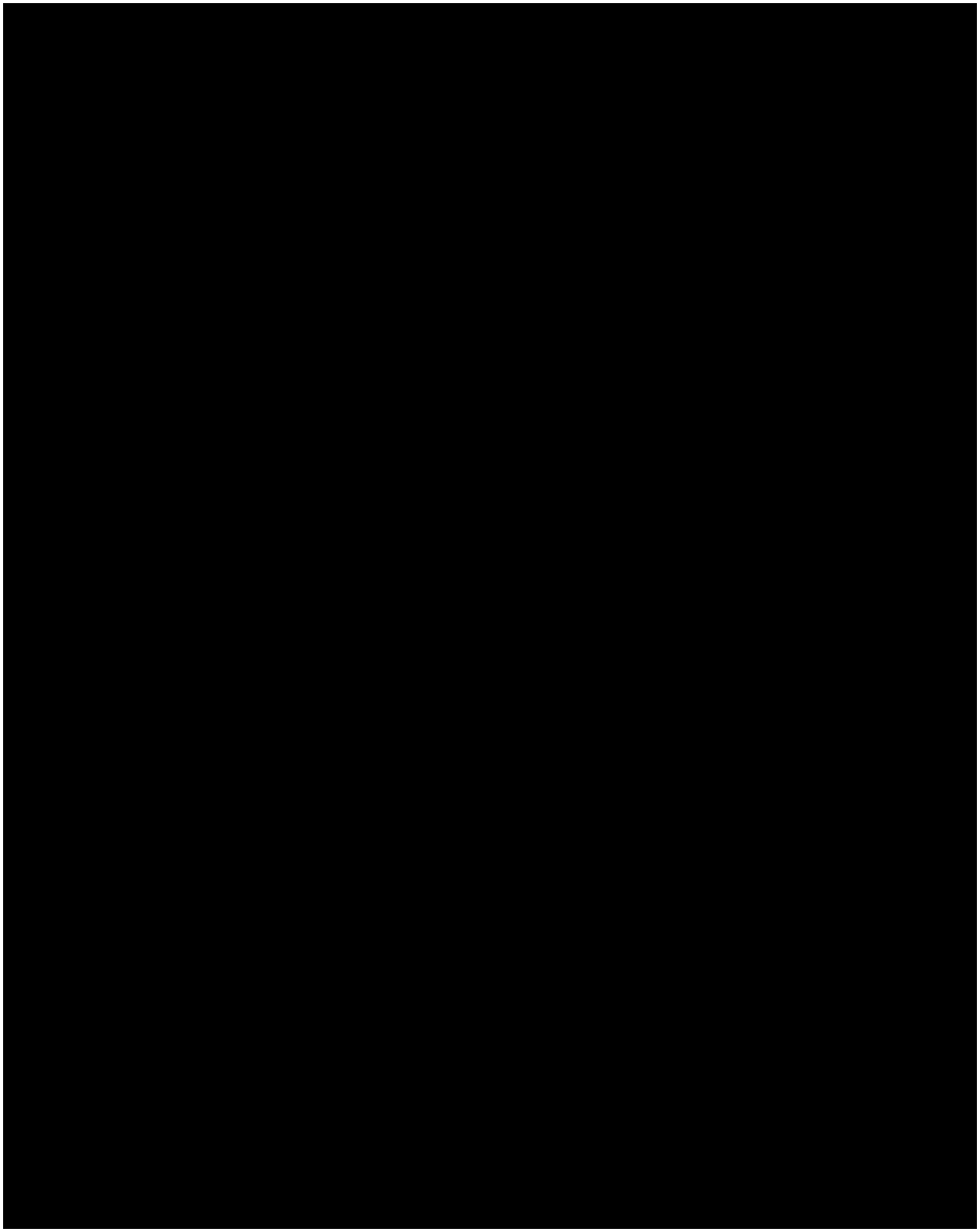
9.1 Changes From the Previous Version of the SAP

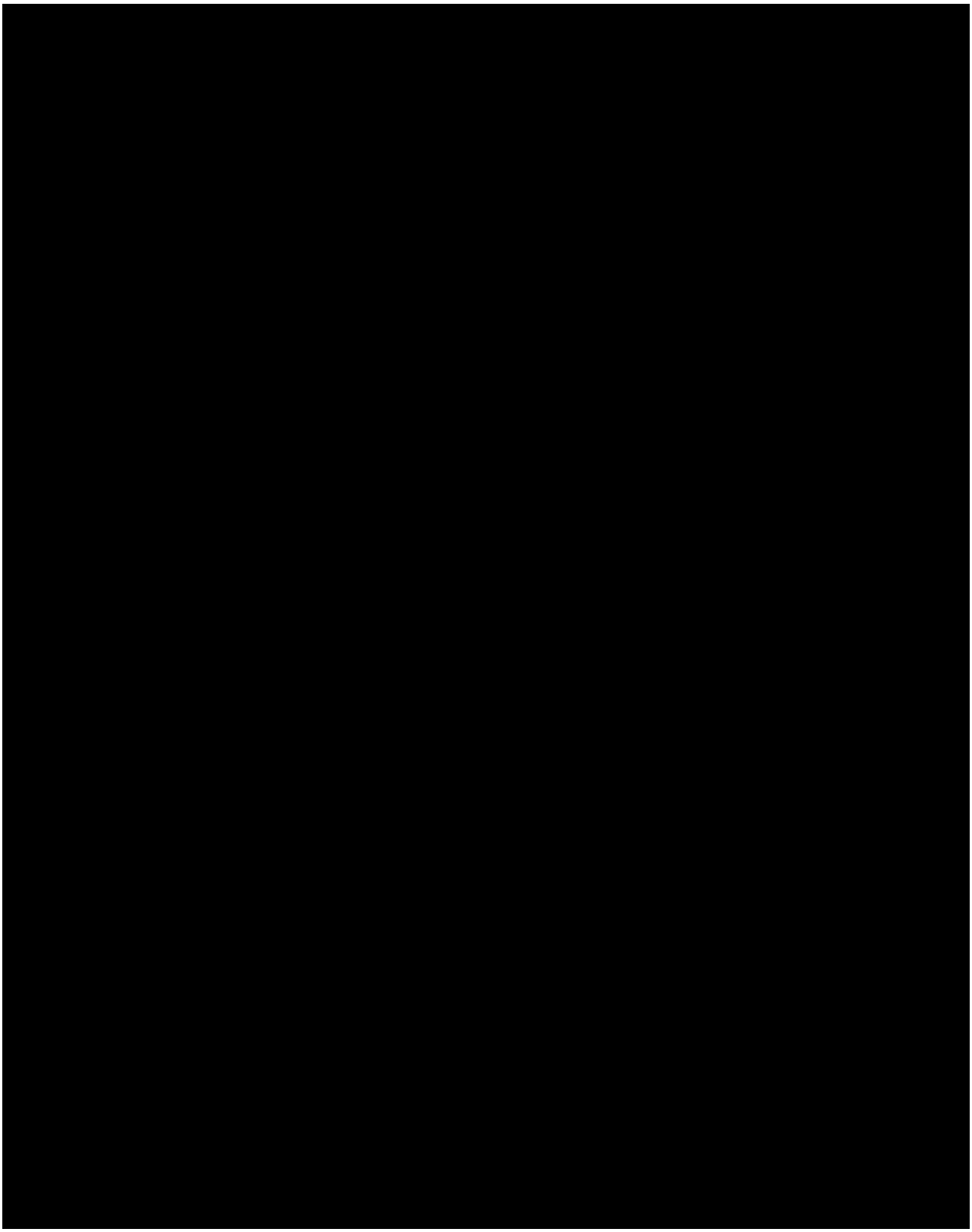
Changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization, and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

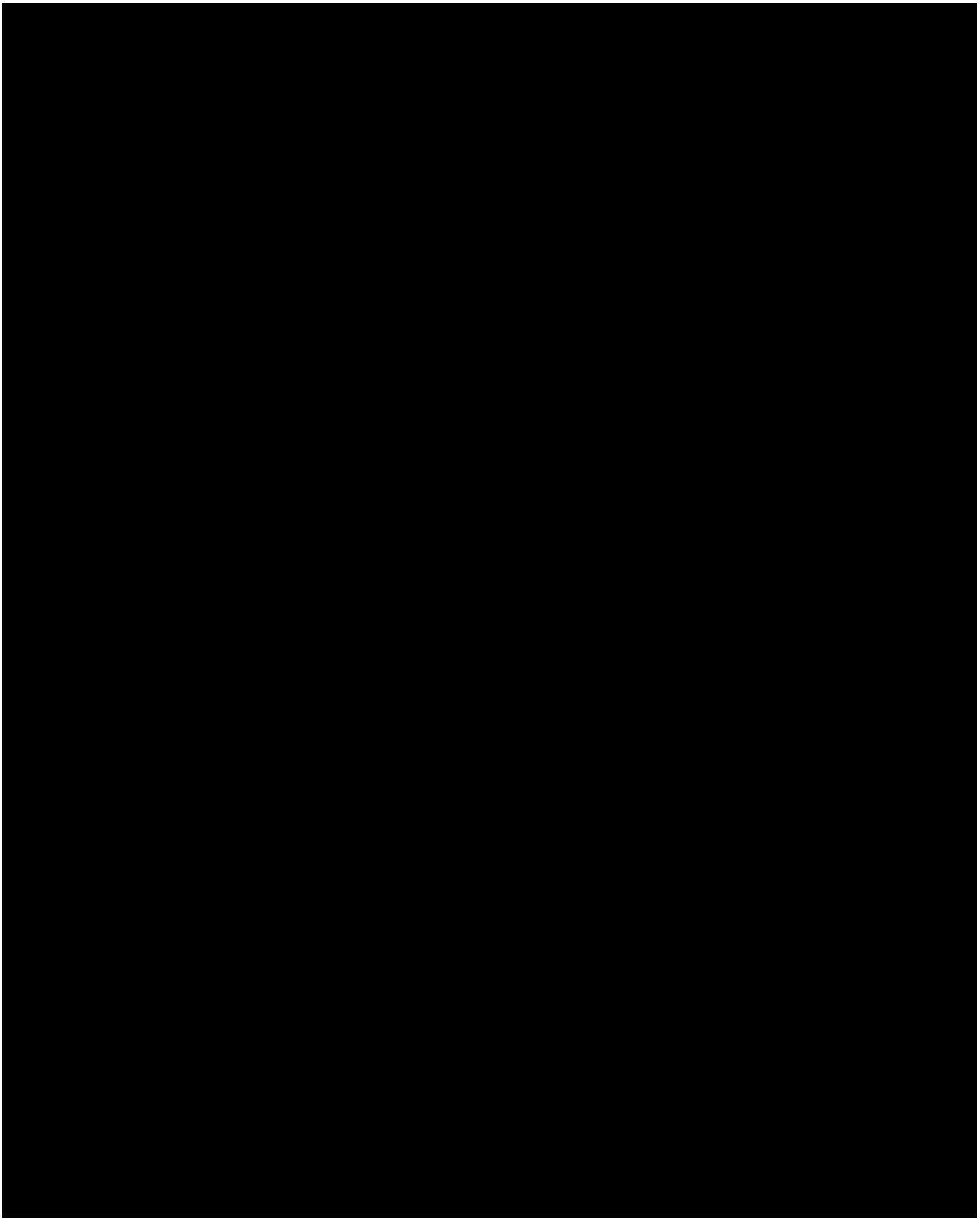
[redacted]

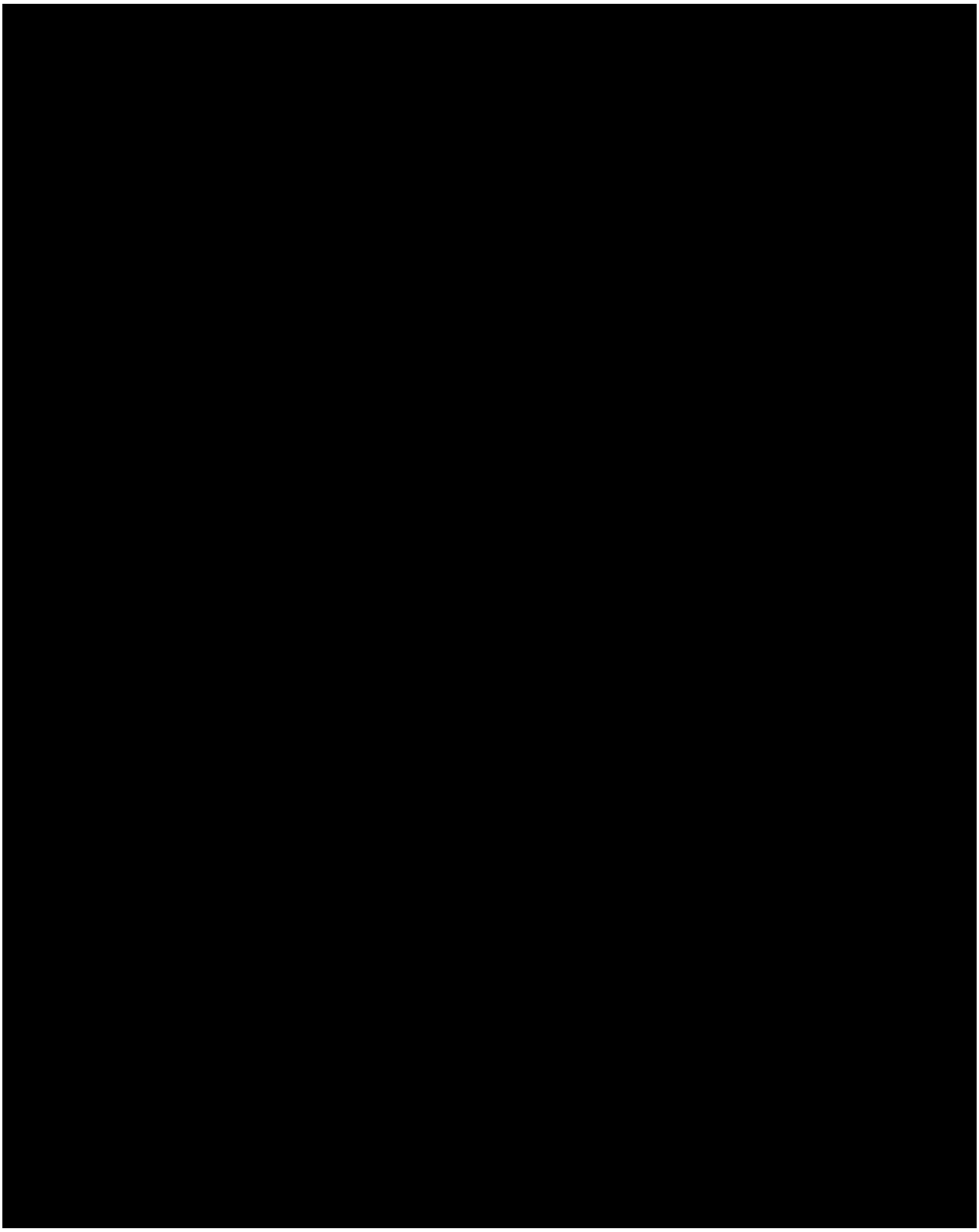


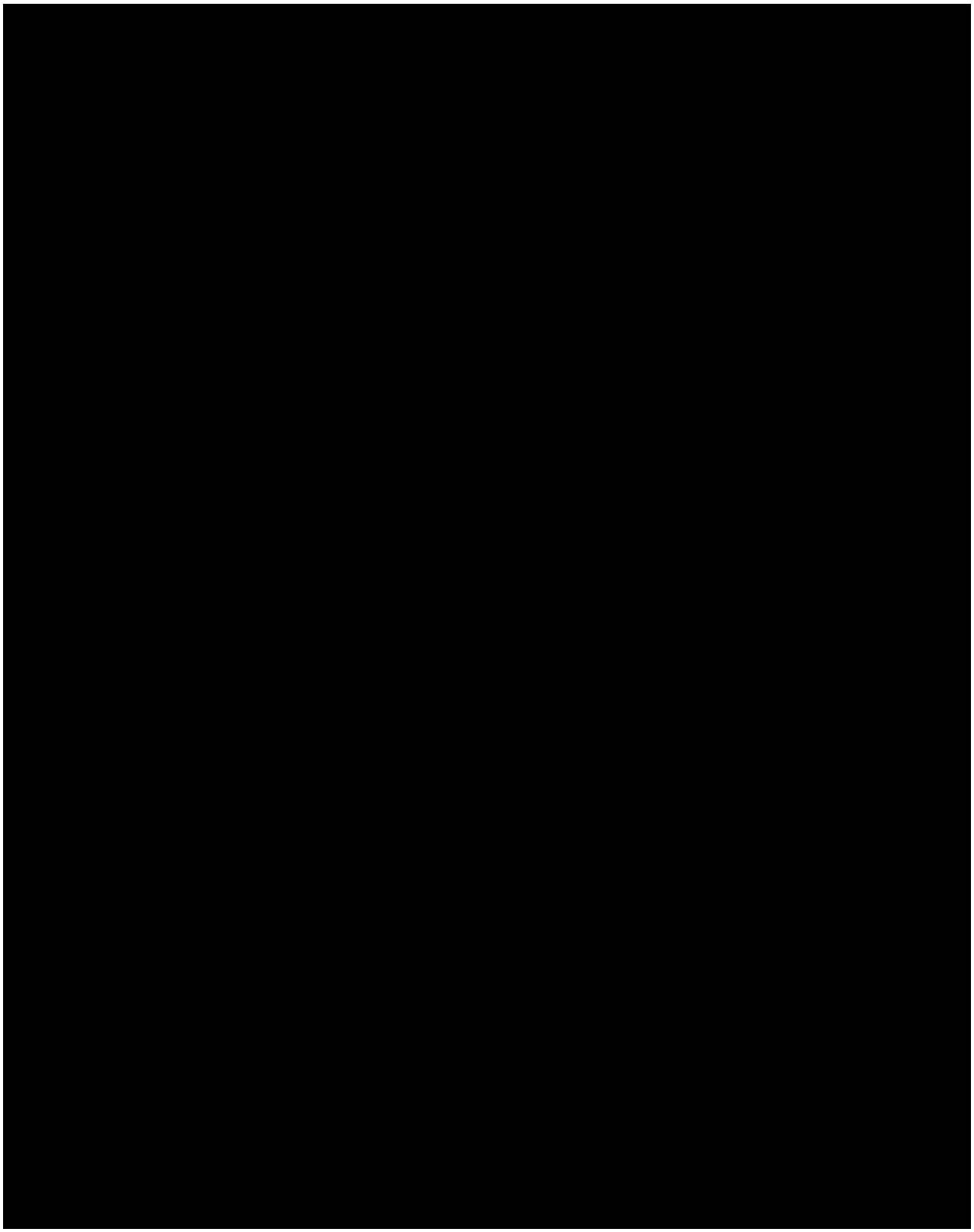


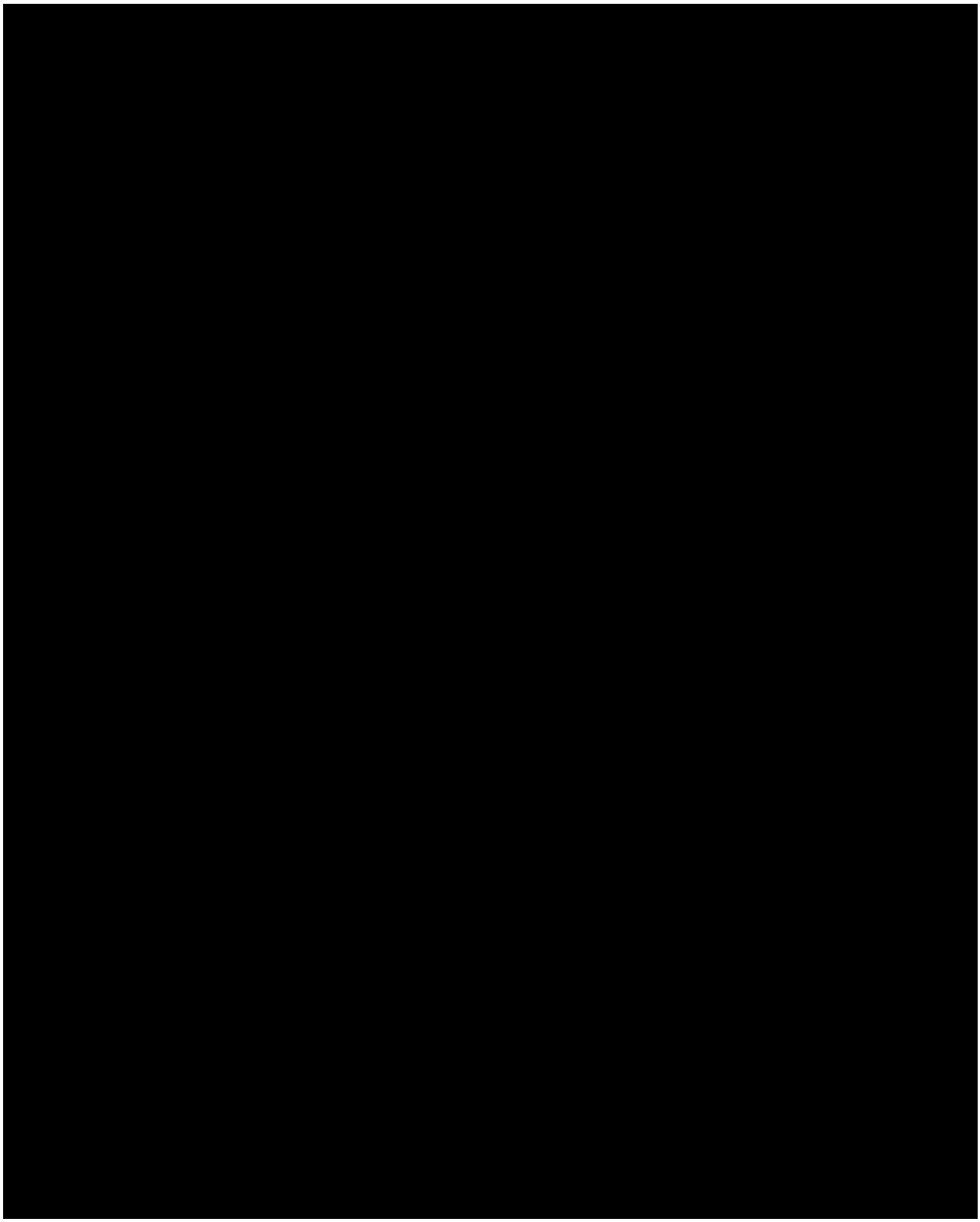












9.2 Data Handling Conventions

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.