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Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE (ADVANCE)

Statistical Analysis Plan Date: June 25, 2020

1 Title Page**STATISTICAL ANALYSIS PLAN****A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND,
PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE
EFFICACY, SAFETY, AND TOLERABILITY OF ORAL ATOGEPANT FOR THE
PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE
(ADVANCE)****Final SAP Date: 13 MAR 2019****Amendment 1: 25 JUN 2020**

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3 List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
AIM-D	Activity Impairment in Migraine - Diary
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	double-blind
eCRF	electronic case report form
ePRO	electronic patient report outcome
ECG	electrocardiogram, electrocardiographic
ET	early termination
██████████	██████████
INR	international normalized ratio
ITT	intent-to-treat
IWRS	interactive web response system
mITT	modified intent-to-treat
MedDRA	Medication Dictionary for Regulatory Activities
██████████	██████████
MMRM	mixed-effects model for repeated measures
MSQ	Migraine Specific Quality of Life Questionnaire
PCS	potentially clinically significant
PDRS	protocol deviation requirement specification
██████████	██████████
PID	participant identification
PT	preferred term
Q1	first quartile (25th percentile of the data)
Q3	third quartile (75th percentile of the data)
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d’Unités (International System of Units)
SOC	standard of care
TBL	total bilirubin
TEAE	treatment-emergent adverse event
WHO	World Health Organization
██████████	██████████

4 Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the protocol amendment #3 (dated 14 May 2020) of Study 3101-301-002. Specifications of tables, figures, and data listings are contained in a separate document.

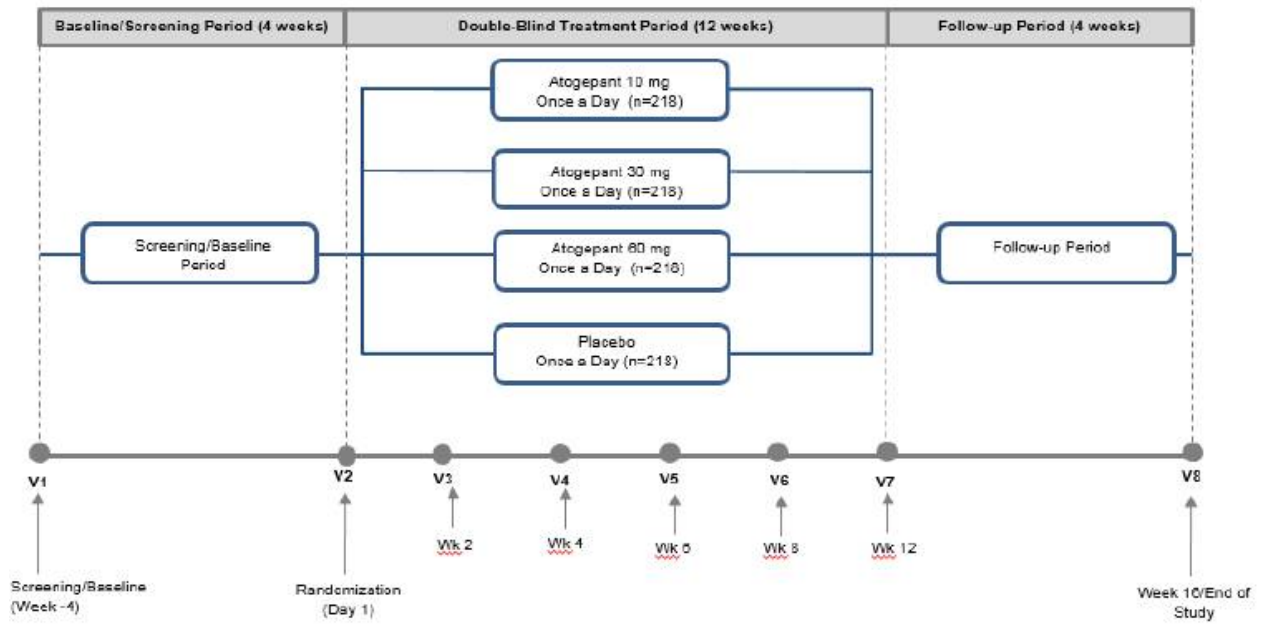
This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study conducted in the United States and will enroll approximately 872 participants from approximately 110 sites. Participants will be randomized to one of four treatment arms (placebo, atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg) in a 1:1:1:1 ratio. Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy. Randomization will be stratified based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy.

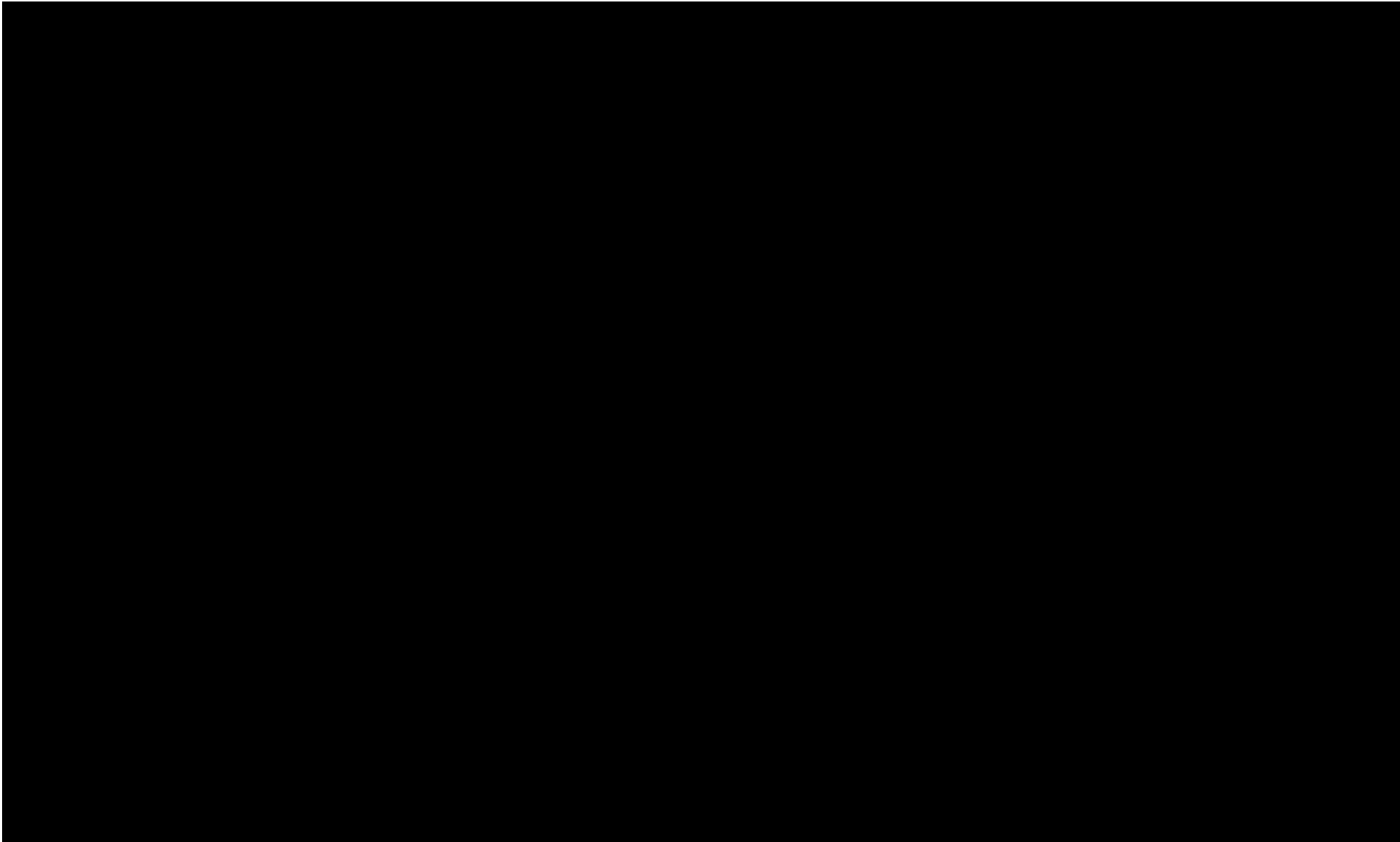
The study will consist of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a follow up period of 4 additional weeks, for a total duration of 20 weeks. Participant participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent follow-up period of 4 additional weeks. There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). The Visit 8 (Follow-up) must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-309-002 (long-term safety extension study). For these participants Visit 8 is not required, as the Follow-up Visit will be performed in the long-term safety study. For participants who screen fail for the long-term safety, the Follow-up Visit must be completed.

Per study design (Protocol Sections 8.4.3.2 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit).

After the last patient first visit on January 31, 2020, COVID-19 pandemic emerged. The Section 0 is added to specify analyses for evaluating the impact of COVID-19.

Figure 4-1 Study Design

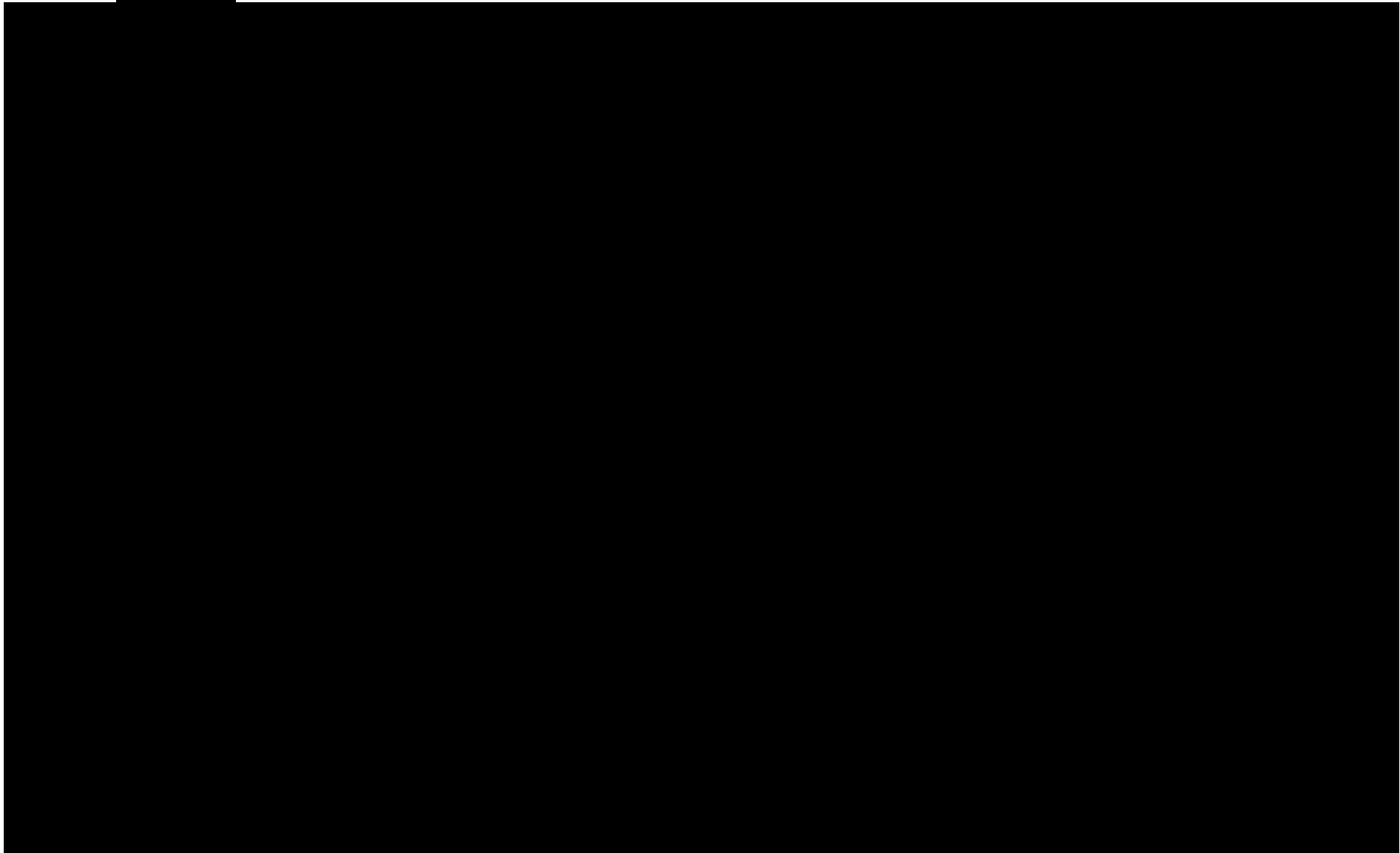


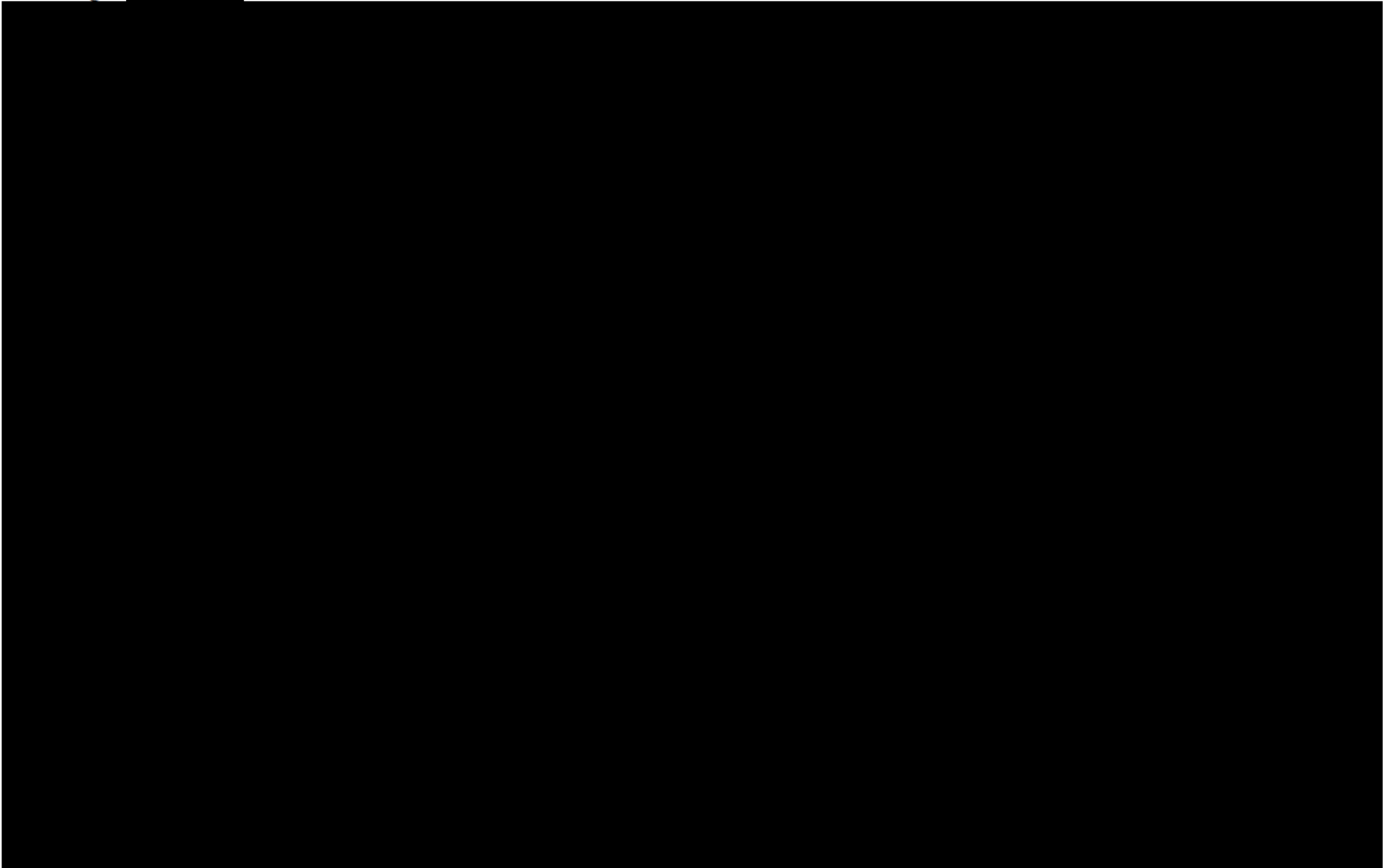




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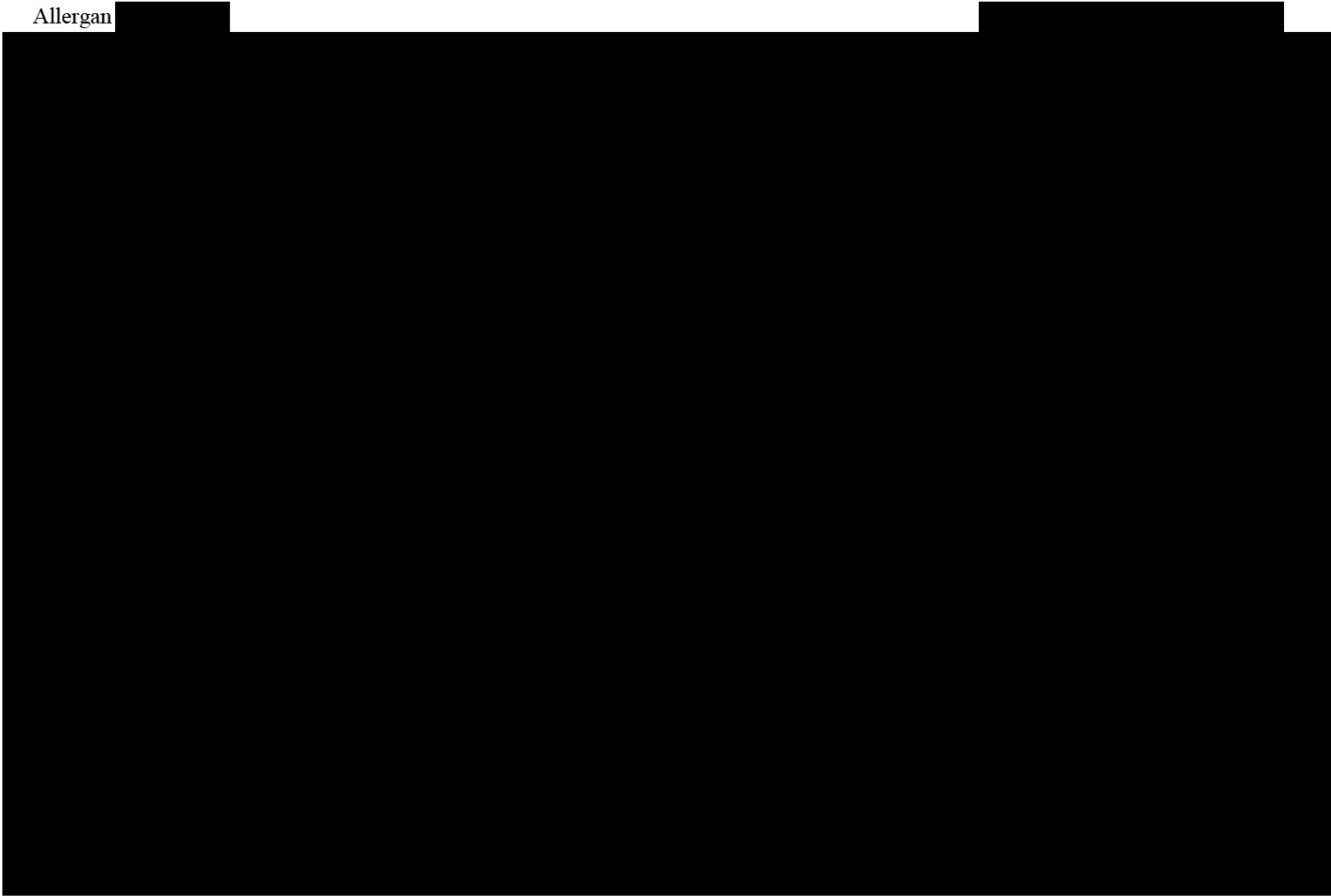
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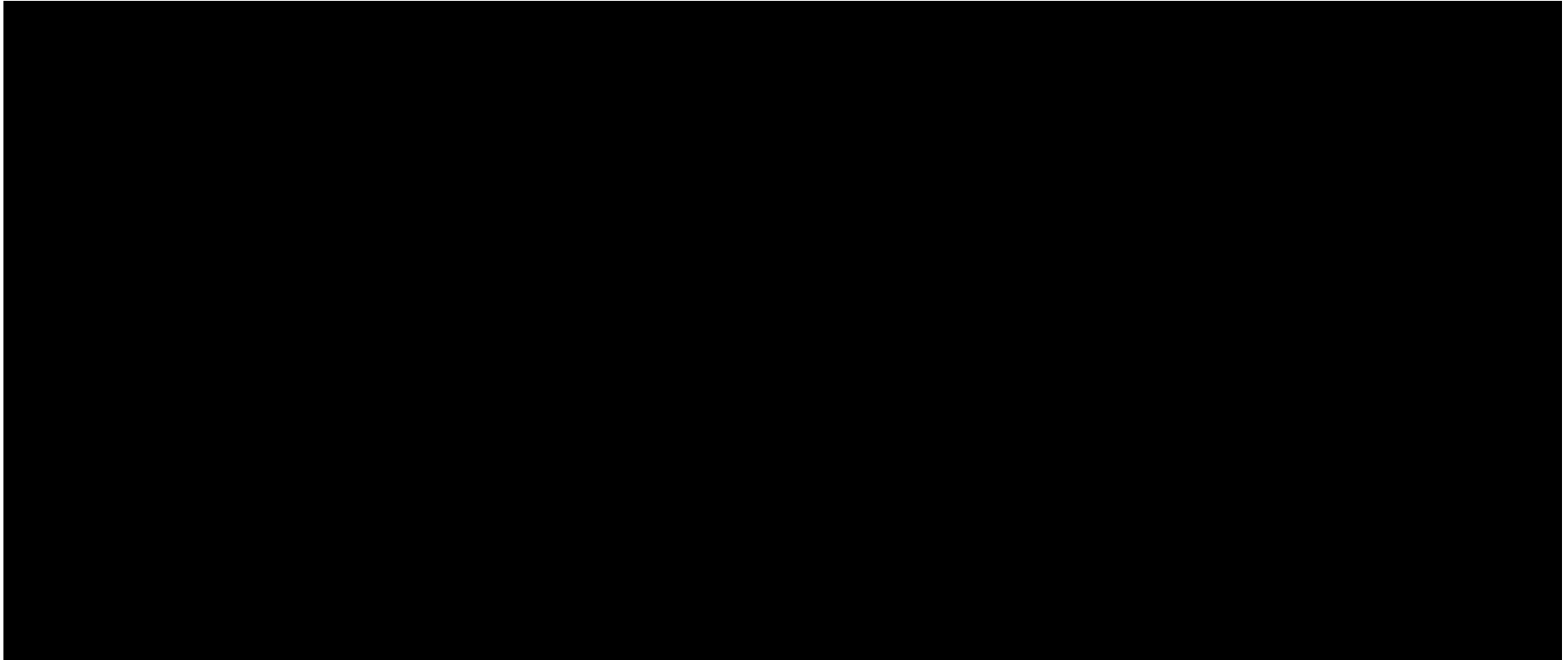




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5 Study Objectives

- To evaluate the safety and tolerability of atogepant 10 mg, atogepant 30 mg and 60 mg for the prevention of migraine in participants with EM.
- To prospectively test for superiority of atogepant 10 mg, atogepant 30 mg and 60 mg versus placebo for the prevention of migraine in participants with EM.

6 Analysis Populations

The analysis populations will consist of participants as defined below.

The Intent-to-Treat (ITT) Population includes all randomized participants.

The Safety Population includes all participants who received at least 1 dose of study intervention. All safety analyses will be performed using the Safety Population and based on the treatment actually received, regardless of assigned treatment according to the planned randomization. Participants will be summarized according to the study treatment received for the majority of treatment period.

The Modified Intent-to-Treat (mITT) Population includes all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All efficacy analyses described in Sections 10.2 - 10.4 will be performed using the mITT population and based on the randomization assignment, regardless of the actual treatment received. All efficacy analyses will be conducted using mITT population unless specified otherwise.

The analysis population for Off-treatment Hypothetical Estimand includes all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the DB treatment period and follow-up period, regardless of whether on study treatment or off study treatment. [REDACTED]

7 Participant Disposition

The number of participants in the ITT, Safety, and mITT Populations will be summarized by treatment group; the number of participants screened will be summarized for overall only. The number of participants in the ITT Population will also be summarized by treatment group for the

following factors: 1) Randomization stratification factor (prior exposure [yes/no] to a migraine prevention medication with proven efficacy) from IWRS; 2) Prior exposure to migraine prevention medication with proven efficacy based on prior medication collected from eCRF, which will be termed as “actual strata” in the SAP. The list of participants with incorrect randomization stratum will be provided.

Screen-failure participants (i.e., participants screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the all screened participants. The number and percentage of participants who enter the double-blind treatment period, complete the double-blind treatment period and of participants who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for all randomized participants. The reasons for premature discontinuation from the double-blind treatment period as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group. The percentage is relevant to the total number of randomized participants. Similar disposition information to the double-blind treatment period will be presented for the follow-up period. All randomized participants who prematurely discontinue during the double-blind treatment period or the follow-up period will be listed by discontinuation reason. The number of participants who signed informed consent for Safety Extension Study 3101-309-002 will be provided.

8 Demographic and Other Baseline Characteristics

Demographic parameters (age; age group [< 20 , 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70]; race; race group [white, all other races]; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as $\text{weight [kg]} / (\text{height [m]})^2$) will be summarized descriptively by treatment group for the Safety and mITT Populations, and Off-treatment Hypothetical Estimand Population. Continuous variables will be summarized by number of participants and mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities, version 22.0 or newer. The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the Safety Population.

Migraine history, including diagnosis, duration of disorder, use of migraine prevention medication in the past, average number of migraine or headache days per month in the last 3

months, acute medications taken to treat migraine headaches, and advice on lifestyle alterations will be reported in total and by treatment group for the Safety Population.

Prior medication is defined as any medication taken before the first dose of double-blind study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of the double-blind study treatment.

Prior medication use will be summarized by the number and proportion of participants in each treatment group receiving each medication within each therapeutic class for the Safety Population. Concomitant medication use will be summarized by the number and percentage of participants in each treatment group receiving each medication within each therapeutic class for the double-blind treatment period and follow-up period for the Safety Population. If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class. Any prior and concomitant medications will be included in listings.

The World Health Organization (WHO) Drug Dictionary Enhanced, March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

Protocol deviations will be defined in Protocol Deviation Requirement Specification (PDRS), including significant classification. The number and percentage of participants with significant protocol deviations will be summarized by treatment group for all categories specified in PDRS for all randomized participants.

Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, Migraine Specific Quality of Life Questionnaire [MSQ] v2.1 Role Function Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D) will be summarized by treatment group for mITT Population and Off-treatment Hypothetical Estimand Population.

9 Extent of Exposure and Treatment Compliance

9.1 Extent of Exposure

Exposure to double-blind study treatment for the Safety Population during the treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of double-blind study treatment taken to the date of the last dose taken, inclusive. The number and percentage of participants with each treatment duration of ≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days will be summarized by treatment group respectively. Descriptive

statistics (number of participants, mean, SD, median, Q1, Q3, minimum, and maximum) will also be summarized by treatment group.

Participant-years, defined as exposure to the study treatment in years, will be summarized by treatment group for the Safety Population.

9.2 Measurement of Treatment Compliance

Dosing compliance for a specified period is defined as the total number of double-blind study medications actually taken by a participant during that period divided by the number of double-blind study medications that were expected to be taken during the same period multiplied by 100. The total number of tablets actually taken during a specific period will be calculated from the study medication record. The prescribed number of tablets during a specific period will be calculated as following: 3 tablets/day \times the number of days during the period. Descriptive statistics for double-blind study medication dosing compliance together with the compliance categories (< 80%, 80% - 120%, > 120%) will be summarized by treatment group for each period between 2 consecutive visits, as well as for the period from the first dose of the double-blind study interventions actually taken to the last dose of double-blind study intervention actually taken for the Safety Population.

10 Efficacy Analyses

10.1 Efficacy and Health Outcome Measures

10.1.1 Efficacy Measures

A migraine day is defined as any calendar day on which a headache occurs which meets criteria A, B, and C **OR** meets criteria D and E, as listed below, as per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

- A. Headache has at least two of the following four characteristics:
 - i. Unilateral location
 - ii. Pulsating quality
 - iii. Moderate or severe pain intensity
 - iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- B. At least one of the following:
 - i. Nausea and/or vomiting
 - ii. Photophobia and phonophobia

- iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
- C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

- D. Any headache which fulfills one criterion from (1) and at least one criterion from (2) **OR** fulfills at least two criteria from (1) and no criteria from (2).

1) Headache characteristics:

- i. Unilateral location
- ii. Pulsating quality
- iii. Moderate or severe pain intensity
- iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

2) Symptoms:

- i. Nausea and/or vomiting
- ii. Photophobia and phonophobia
- iii. Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

- E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Note that antiemetics will not be counted as an acute headache medication for headache day identification. Calendar days begin at midnight and last until 11:59 PM (23:59).

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The allowed medications include the following categories of drugs: triptans, ergots, opioids, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a participant reports intake of a triptan to treat a migraine per participant diary.

Headache day pain intensity is defined as the worst pain intensity on any headache day where headache pain intensity will be subjectively rated by the patient on a scale from mild to severe:

- Mild pain (=1)
- Moderate pain (=2)
- Severe pain (=3)

If participants experience no headache in a day, then the corresponding pain intensity of that day will be set as missing.

10.1.2 Health Outcome Measures

The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (i.e., difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (i.e., difficulty walking, moving body, bending forward, moving head) using a 6-point rating scale ranging from “Not difficult at all,” “A little difficult,” “Somewhat difficult,” “Very difficult,” “Extremely difficult,” and “I could not do it at all.” Three items include a response of “I did not...,” for example, “I did not have errands planned.” The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with “during your headache” indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (i.e., higher disease burden).

Two items based on a 24-hour recall will be administered daily using Headache and Non-headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5-level response scale ranging from “No activity – Spent all day lying down” to “Exercised – Brisk

walk, running, jogging, biking or other activity for 30 or more minutes.” The second item will be used to evaluate activity limitation with a 5-level response scale ranging from “Not at all limited – I could do everything” to “Extremely limited”.

[REDACTED]

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past 4 weeks. It is divided into three domains: Role Function Restrictive assesses how migraines limit one’s daily social and work-related activities; Role Function Preventive assesses how migraines prevent these activities; and the Emotional Function domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from “none of the time” to “all of the time.” Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.

[REDACTED]

10.2 Primary Efficacy Endpoints

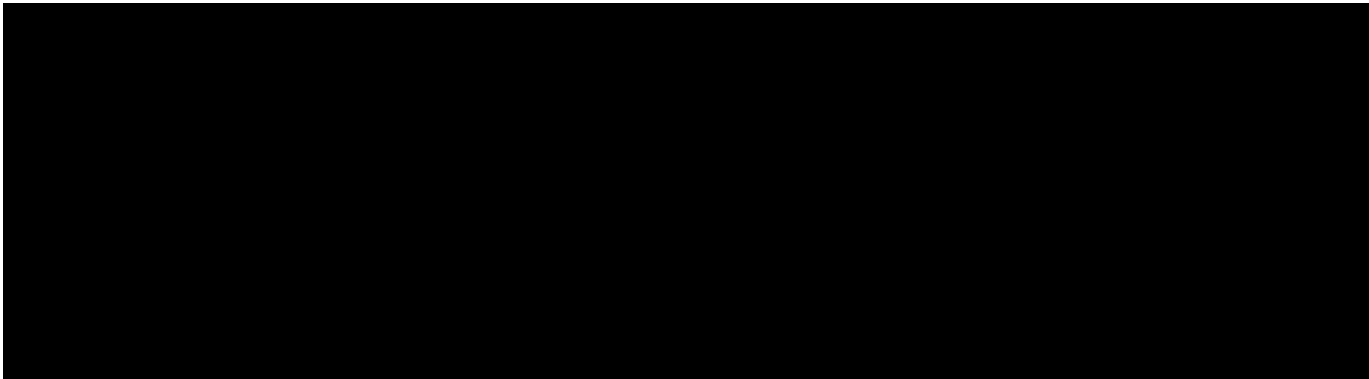
The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period. The primary null hypothesis is that atogepant treatment doses (atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once a day) are each equally effective to placebo in mean change from baseline in mean monthly migraine days across the 12-week treatment period. The alternative hypothesis is that at least 1 of the 3 doses of atogepant has a different effect than placebo. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date.

10.2.1 Primary Analysis [REDACTED]

The endpoint will be analyzed using a mixed model for repeated measures (MMRM). The response variable is the change from baseline to each postbaseline month in monthly migraine days. The model will include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. The stratum “prior exposure (Yes/No)” will use the actual stratification factor from prior medication collected by eCRF. The analysis will be performed based on evaluable postbaseline data using only the observed cases without missing data imputation. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization.

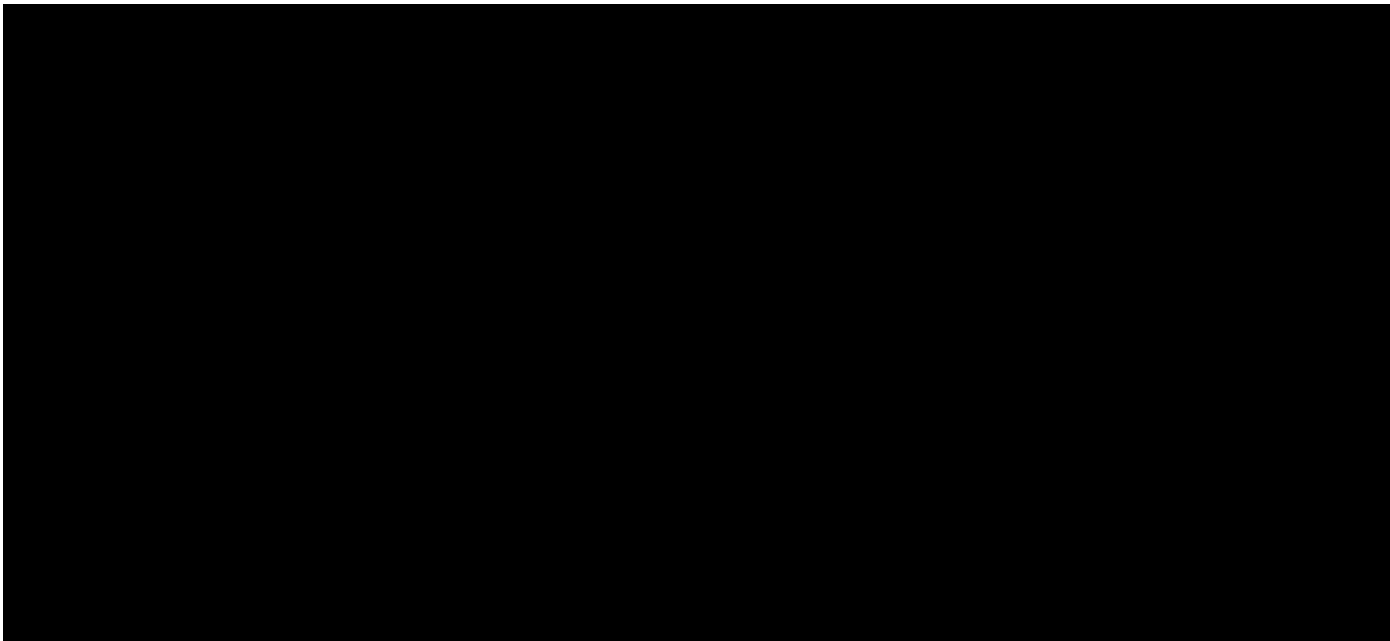
Restricted maximum likelihood method will be used. The within-patient correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the Toeplitz covariance structure will be used. If the model with the Toeplitz covariance structure does not converge, then the compound symmetry covariance structure will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Contrasts will be constructed to obtain the average treatment effects across the 12-week treatment period to compare each atogepant treatment group versus the placebo group. Each

treatment effect and treatment comparisons will be estimated by the LS Means and their differences in LS Means, along with their SE and 95% confidence intervals, and the p-value corresponding to the between-treatment group difference. The sample SAS code is given as follows



The impact of dropouts on the primary efficacy measure will be explored graphically by plotting the response profiles by the dropout reason. Plot of mean change from baseline in the number of migraine days versus visit (month) based on the observed cases will be provided in each treatment group by major reason of early termination, such as, adverse events, lack of efficacy, withdrawal of consent, lost to follow-up, etc. Similar plot for completers in each treatment group will be provided as a reference.

10.2.2 Sensitivity Analysis for Possible Violation of Normality Assumption



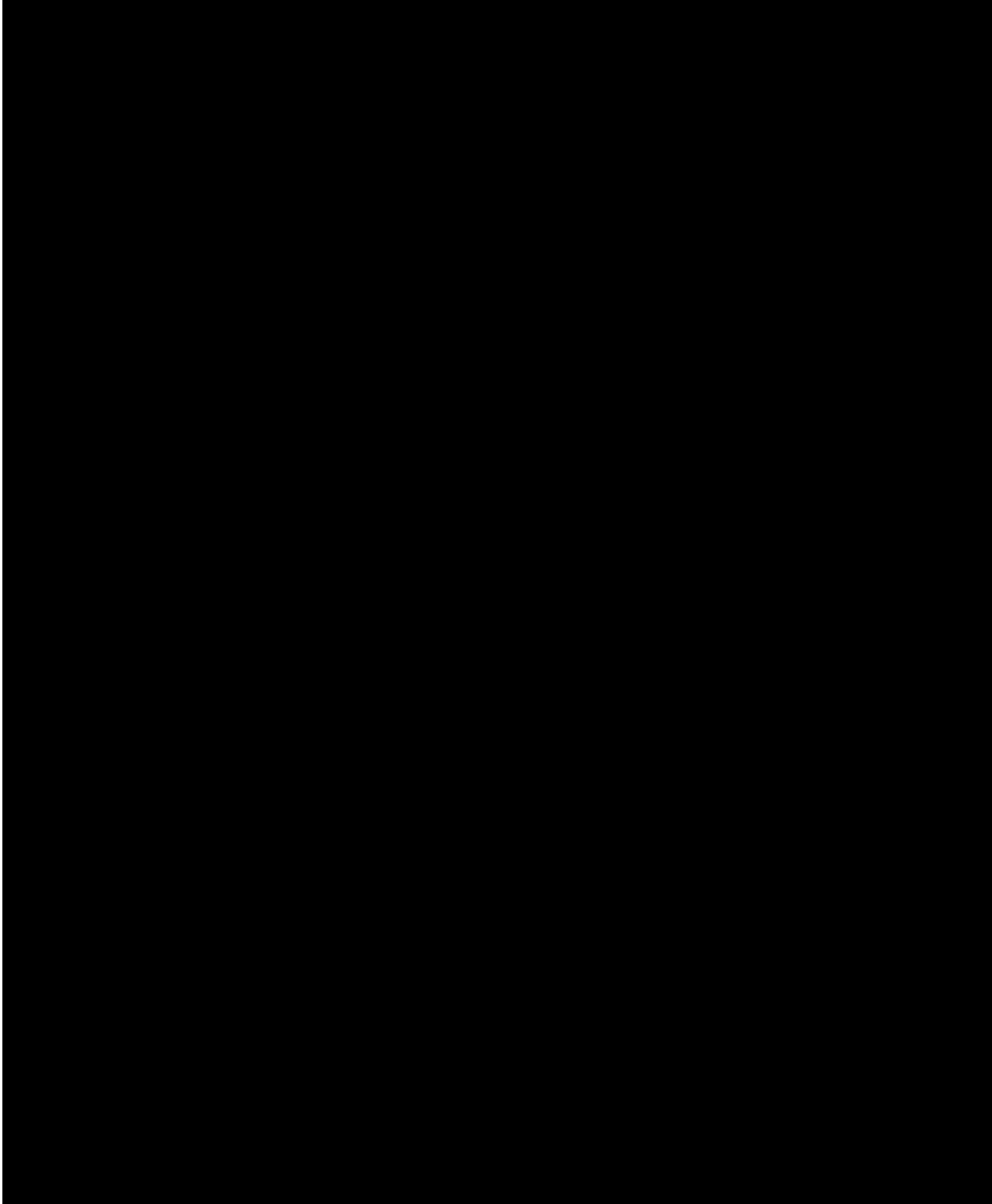
10.2.3 Sensitivity Analyses in Missing Data Handling

ANCOVA Model Based on 3-month Average of the Monthly Migraine Days

The response variable for the ANCOVA model is the change from baseline in the 3-month average of the monthly migraine days for each participant. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. This analysis was recommended by FDA at the End of Phase 2 meeting and termed as supportive analysis. There are no missing data based on this derivation because patients who discontinued the treatment are assumed to maintain the same mean (observed while on treatment) for 3 months (12 weeks).

Within-group Imputation Based on Observed Data

Sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. The details of imputation are as follows



MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods

The details for this analysis are provided in Section 10.5.

10.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints for the United States and the EU are as follows:

- Change from baseline in mean monthly headache days across the 12-week treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period.
- $\geq 50\%$ reduction in 3-month average of monthly migraine days
- Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12.
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.
- Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period.

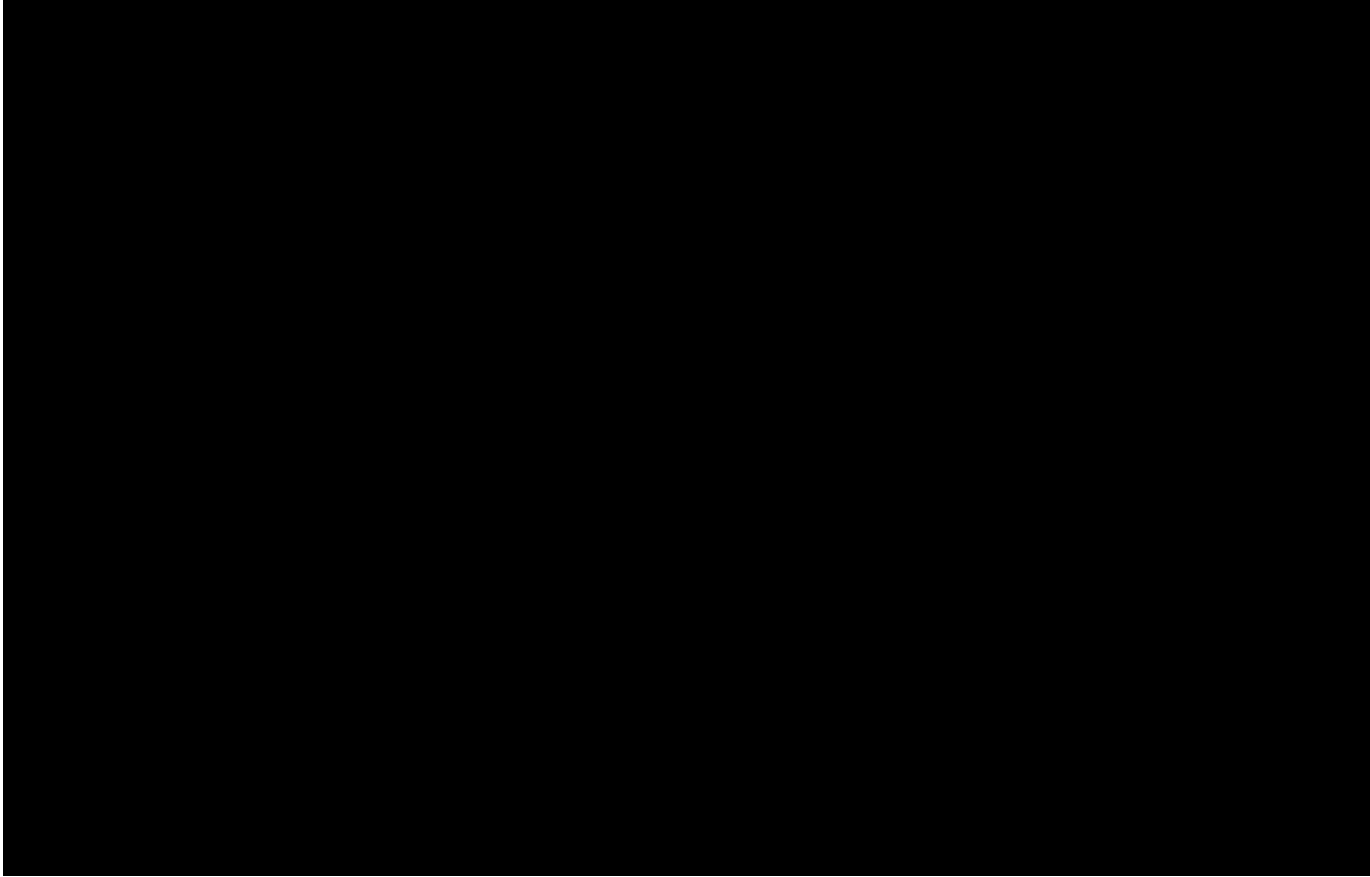
The secondary endpoints for headache days, acute medication use days, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint. For MSQ v2.1 Role Function Restrictive domain score, the analysis will be performed similarly to the primary MMRM, with focus on the pairwise contrasts of each dose group to placebo at Week 12. Week

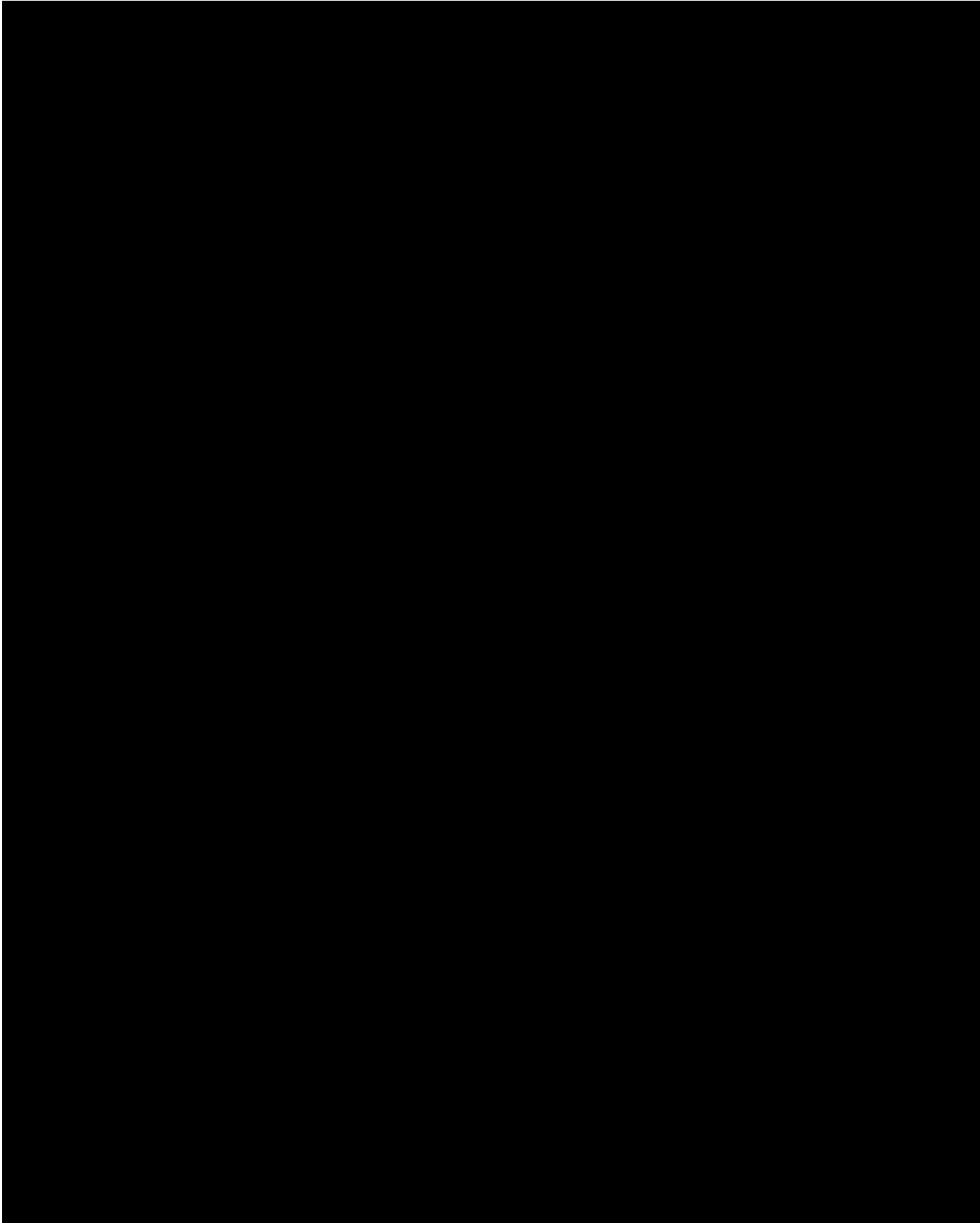
16 (follow-up visit) data for MSQ v2.1 Role Function Restrictive domain score will not be included in MMRM analysis, and only summary statistics for Week 16 will be provided. The corresponding sample SAS code is given as follows

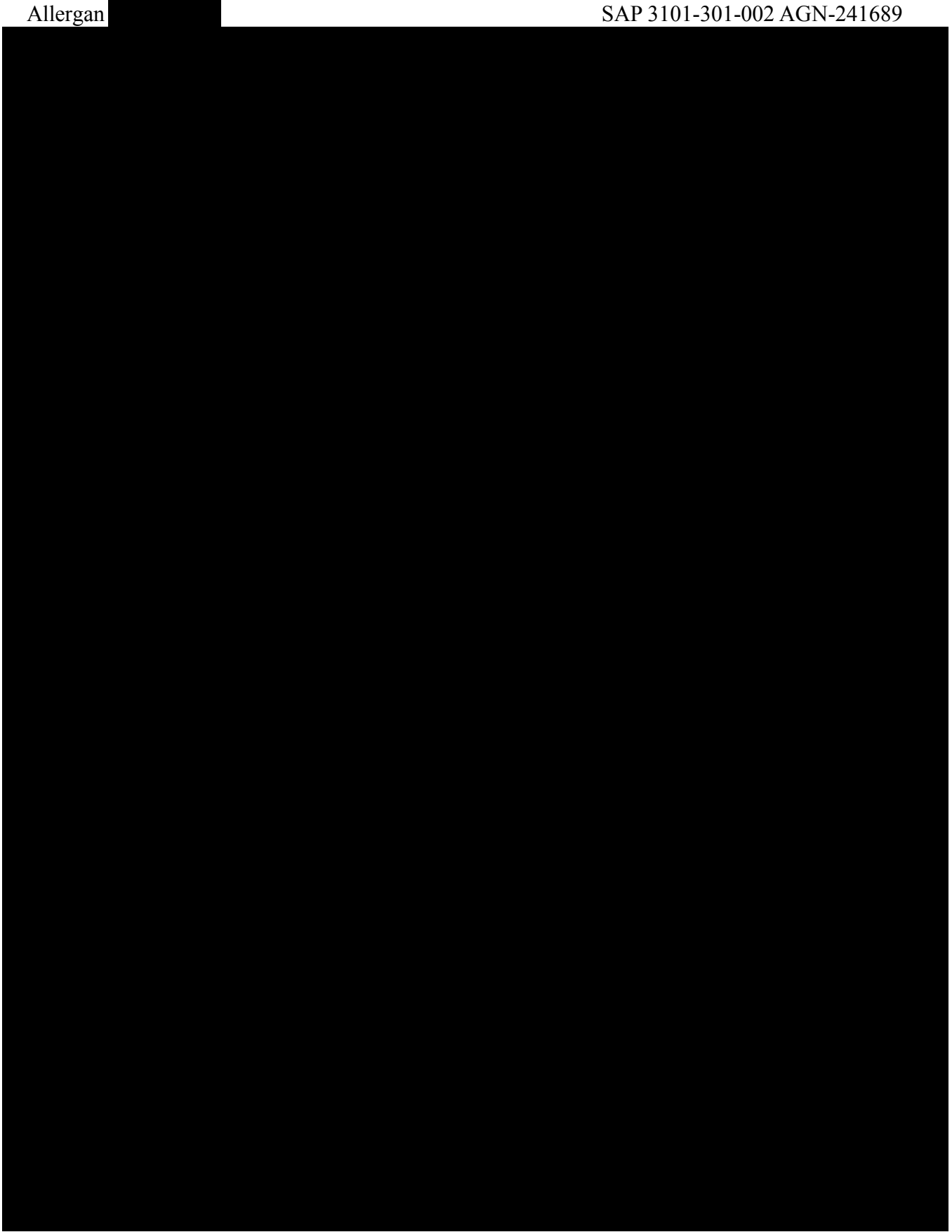
[REDACTED]

The 50% responder, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model. The sample SAS is given as follows

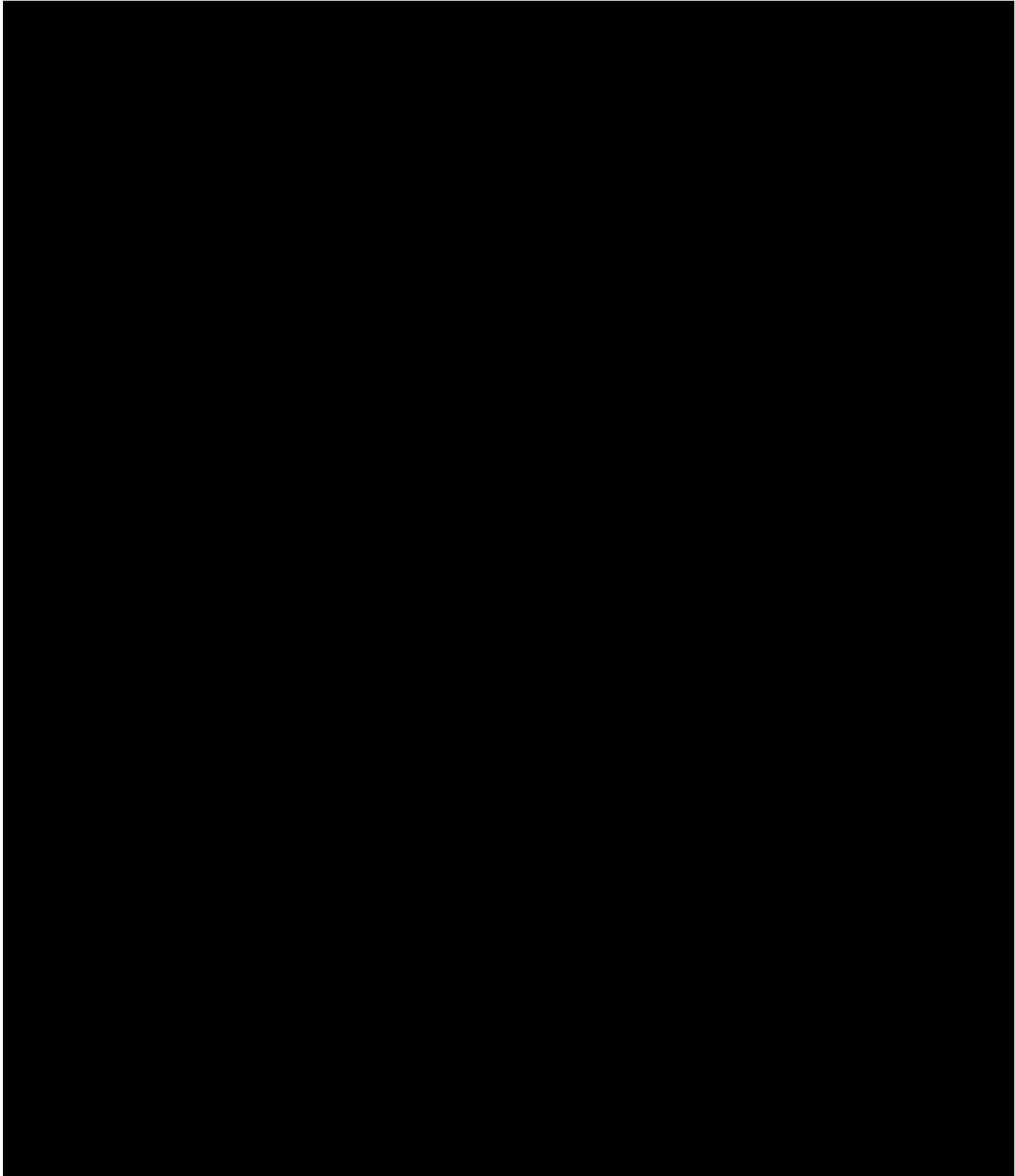
[REDACTED]

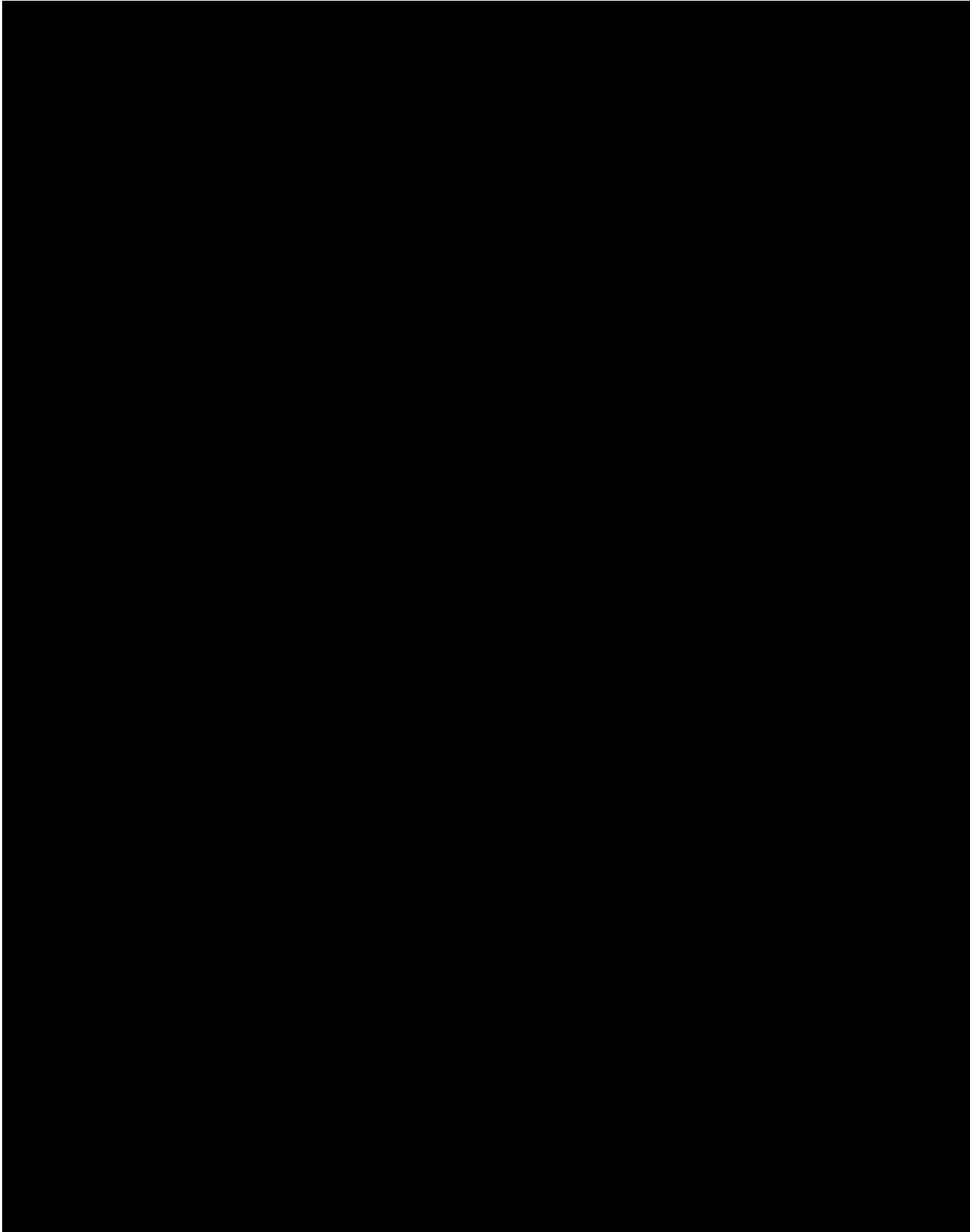


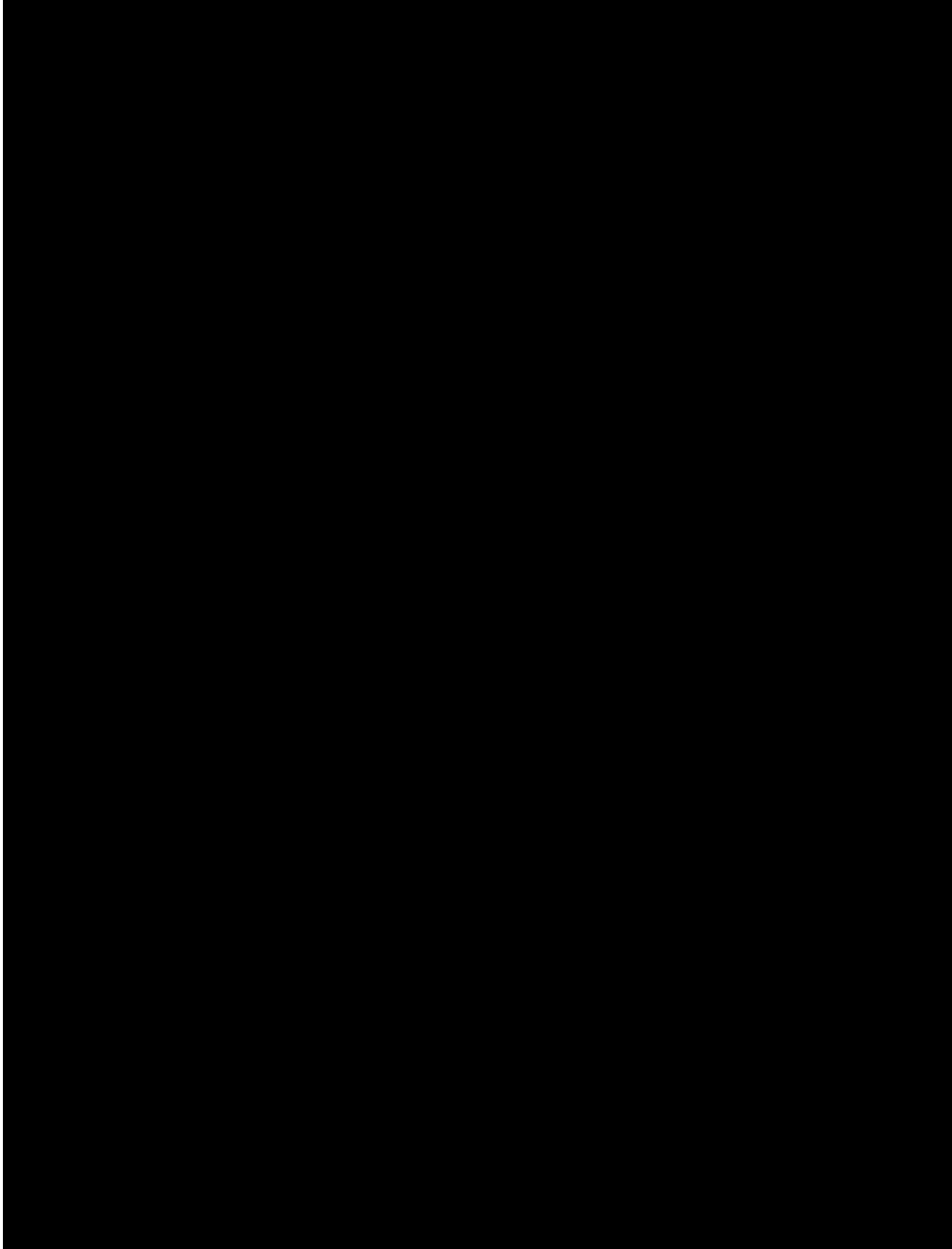




10.4 Additional Endpoints







10.5 Off-treatment Hypothetical Estimand

This section defines an estimand [REDACTED]

Per study design (Protocol Sections 8.4.3.1 and 8.8), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit), i.e., participants who prematurely discontinued (before Week 12) will continue to complete eDiary efficacy assessments while off-treatment.

10.5.1 Treatment Condition of Interest

Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited medications are described below:

- Participants are allowed to take acute migraine medications (Protocol Section 4.4.1) to keep the participants in the study.
- The protocol prohibits patients from starting any new migraine preventive treatments (Protocol Section 4.4.2) during the study (including the double-blind treatment period and the follow-up period).

10.5.2 Population

The target population is patients suffering from migraine with aura or migraine without aura satisfying the inclusion and exclusion criteria as specified in Section 4 of protocol.

The analysis population for off-treatment hypothetical estimand is defined to be all randomized participants who received at least 1 dose of study treatment, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data, regardless of whether on study treatment or off study treatment.

[REDACTED] On study treatment is from the first dose till the last dose of study intervention. As the analysis-visit mapping window (Table 17–2) is defined for the entire postbaseline period (not limited to the double-blind treatment period for participants who prematurely discontinued), the number of participants in the analysis population for off-treatment hypothetical estimand is expected to be greater than or equal to the number of participants in the mITT Population.

10.5.3 Variable

The variable is the same as the primary efficacy endpoint defined in Section 10.2, which is the change from baseline in the participant's mean monthly (4-weeks) migraine days across the 12-week treatment period as derived from the eDiary data.

10.5.4 Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data during the follow-up period after starting the new migraine prophylaxis treatment excluded from the analysis.
- Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.

If a participant provides less than 14 days of efficacy data during a monthly period regardless in the double-blind treatment period or the follow-up period, then he/she is considered to have missing data during that monthly period. When a participant provides at least 14 days of efficacy

data during a monthly period, he/she is considered to have efficacy data during that monthly period.

As the protocol prohibits participants from starting any new prophylaxis treatment until the study is completed. Only a limited number of participants as protocol deviators might take new prophylaxis treatment during the study. The criteria for identifying the participants who started a new migraine prophylaxis treatment are described in Section 17.11.

10.5.5 Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each atogepant group and placebo.

Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, an MMRM similar to the primary analysis specified in Section 10.2.1 will be performed on observed data collected from both double-blind treatment period and follow-up period. The model terms include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, treatment- by-visit interaction, the baseline score and baseline-by-visit interaction.

10.5.6 Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints

Continuous secondary endpoints based on eDiary data will be handled using the same estimand approach defined above for the primary endpoint.

The secondary endpoint of 50% responders are derived at least a 50% reduction from baseline in the 3-month average of monthly migraine days using data collected from the double-blind period and follow-up period. Data after participants started a new prophylaxis treatment during the follow-up period will be excluded. The population-level summary for this endpoint is the odds ratio from a logistic regression for each atogepant group relative to placebo with baseline monthly migraine days as a covariate, prior exposure (yes/no) to a migraine prevention medication with proven efficacy and treatment group as fixed factors.

The graphical approach to control the overall Type I error rate described in Section 10.3 will be provided for primary and key secondary endpoints in the analysis population for off-treatment hypothetical estimand.

11 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For clinical laboratory, vital sign, and ECG, the last non-missing safety assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or newer.

An AE will be considered as a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date of the first dose of double-blind study treatment. An AE that occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore, TEAEs can be identified as those AEs captured in Study 3101-301-002 with recorded onset date on or after the date of the first dose of double-blind study treatment and within 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later. An AE will be considered as a treatment-emergent SAE (TESAE) if it is a TEAE that also meets SAE criteria. TEAEs that started after the date of last dose of study treatment will be considered as newly emergent.

Only AEs captured in Study 3101-301-002 will be considered for TEAEs in this study. For participants rolling over into Study 3101-309-002 (extension study) who start the first dose on Visit 1 or beyond, AEs captured in Study 3101-309-002 will be summarized in that study although some AEs might occur within 30 days after the last dose from Study 3101-301-002.

Overall summary of AEs will be provided on a per-participant basis for categories of TEAEs, treatment-related TEAEs, deaths, TESAEs, and TEAEs leading to treatment discontinuation.

The number and percentage of participants reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term, and further categorized by severity to the study treatment.

The number and percentage of participants reporting treatment-related TEAEs in each treatment group will be tabulated by system organ class and preferred term.

The number and percentage of participants reporting newly emergent TEAEs in each treatment group will be tabulated by system organ class and preferred term.

The number and percentage of participants who have TEAEs leading to treatment discontinuation will be summarized by system organ class, preferred term and treatment group.

The incidence of common ($\geq 2\%$ of participants in any treatment group) TEAEs will be summarized by preferred term, and treatment group. A similar 5% table will be provided as well.

The number and percentage of participants who have TESAE in each treatment group will be tabulated by system organ class and preferred term.

In addition, separate tabular displays will be presented for patients who died, participants with SAEs, and participants with TEAEs leading to treatment discontinuation.

11.2 Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group for the following laboratory parameters:

Hematology:	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Chemistry:	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, eGFR
Urinalysis:	Specific gravity, pH

In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters

listed in [Appendix I](#). A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of [Appendix I](#).

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in [Table 11–1](#). The normal range for eGFR was not collected in the lab. Therefore, $eGFR < 60 \text{ mL/min/1.73m}^2$ is defined in [Table 11–2](#) to classify renal function as the category of “Moderate eGFR Decrease or Worse” based on FDA guidance on PK studies in Patients with impaired renal function. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value during the study. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of the double-blind treatment period for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by the laboratory vendor.

Potential Hy’s Law criteria within a 24-hour window is defined by a post baseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times \text{ULN}$, along with total bilirubin (TBL) $\geq 2 \times \text{ULN}$ and a non-elevated alkaline phosphatase (ALP) $< 2 \times \text{ULN}$, all based on blood draws collected within a 24-hour period. Potential Hy’s Law criteria without time window is defined by maximum of post baseline elevation of ALT or AST $\geq 3 \times \text{ULN}$, along with maximum of post baseline elevation of TBL $\geq 2 \times \text{ULN}$. Patients who meet the potential Hy’s Law criteria from the first dose of study drug to the end of study will be summarized. Supportive tabular displays will also be provided.

Table 11–1 **Criteria for Potentially Clinically Significant Laboratory Values**

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	$< 0.8 \times \text{LLN}$	$> 1.2 \times \text{ULN}$
	Alanine aminotransferase	U/L	—	$\geq 3.0 \times \text{ULN}$
	Alkaline phosphatase	U/L	—	$\geq 3.0 \times \text{ULN}$
	Aspartate aminotransferase	U/L	—	$\geq 3.0 \times \text{ULN}$
	Bicarbonate	mmol/L	$< 0.9 \times \text{LLN}$	$> 1.1 \times \text{ULN}$
	Bilirubin, total	$\mu\text{mol/L}$	—	$\geq 1.5 \times \text{ULN}$
	Blood urea nitrogen	mmol/L	—	$> 1.5 \times \text{ULN}$
	Calcium	mmol/L	$< 0.9 \times \text{LLN}$	$> 1.1 \times \text{ULN}$

Table 11–1 Criteria for Potentially Clinically Significant Laboratory Values

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	μmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m ²	< 60	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	μmol/L	—	> 1.2 × ULN
	Hematology	Basophils, absolute cell count	10 ⁹ /L	—
Eosinophils, absolute cell count		10 ⁹ /L	—	> 2.0 × ULN
Hematocrit		Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin		g/L	< 0.9 × LLN	> 1.1 × ULN
Lymphocytes, absolute cell count		10 ⁹ /L	< 0.7 × LLN	> 1.3 × ULN
Monocytes, absolute cell count		10 ⁹ /L	< 0.5 × LLN	> 2.0 × ULN
Neutrophils, absolute cell count		10 ⁹ /L	< 0.7 × LLN	> 1.3 × ULN
Platelet count		10 ⁹ /L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count		10 ¹² /L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count		10 ⁹ /L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis		pH	pH	< 0.9 × LLN
	Glucose	—	—	At least 1+
	Protein	—	—	At least 1+
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory.

SI = Le Système International d'Unités (International System of Units).

eGFR < 60 mL/min/1.73m² indicates moderate eGFR decrease or worse.

The number and percentage of participants meeting each of the following criteria for postbaseline hepatic laboratory abnormalities listed in [Table 11–2](#) will be summarized by treatment group. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

Table 11-2

Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	$\geq 1 \times \text{ULN}$
	$\geq 1.5 \times \text{ULN}$
	$\geq 2 \times \text{ULN}$
	$\geq 3 \times \text{ULN}$
	$\geq 5 \times \text{ULN}$
	$\geq 10 \times \text{ULN}$
	$\geq 20 \times \text{ULN}$
AST	$\geq 1 \times \text{ULN}$
	$\geq 1.5 \times \text{ULN}$
	$\geq 2 \times \text{ULN}$
	$\geq 3 \times \text{ULN}$
	$\geq 5 \times \text{ULN}$
	$\geq 10 \times \text{ULN}$
	$\geq 20 \times \text{ULN}$
ALT or AST	$\geq 1 \times \text{ULN}$
	$\geq 1.5 \times \text{ULN}$
	$\geq 2 \times \text{ULN}$
	$\geq 3 \times \text{ULN}$
	$\geq 5 \times \text{ULN}$
	$\geq 10 \times \text{ULN}$
	$\geq 20 \times \text{ULN}$
Bilirubin Total	$\geq 1 \times \text{ULN}$
	$\geq 1.5 \times \text{ULN}$
	$\geq 2 \times \text{ULN}$
	$\geq 3 \times \text{ULN}$
	$\geq 5 \times \text{ULN}$
	$\geq 10 \times \text{ULN}$
	$\geq 20 \times \text{ULN}$
Alkaline Phosphatase	$\geq 1 \times \text{ULN}$
	$\geq 1.5 \times \text{ULN}$
	$\geq 2 \times \text{ULN}$
	$\geq 3 \times \text{ULN}$
	$\geq 5 \times \text{ULN}$
	$\geq 10 \times \text{ULN}$
	$\geq 20 \times \text{ULN}$
Concurrent Elevations ¹	ALT or AST $\geq 3 \times \text{ULN}$ and Bilirubin Total $\geq 1.5 \times \text{ULN}$
	ALT or AST $\geq 3 \times \text{ULN}$ and Bilirubin Total $\geq 2 \times \text{ULN}$
Potential Hy's Law ¹	ALT or AST $\geq 3 \times \text{ULN}$ and Bilirubin Total $\geq 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase;
 ULN = upper limit of normal (value provided by the laboratory).

¹ Elevations are from the same day

The number and percentage of participants with an adjudicated case (i.e., ALT $\geq 3 \times$ ULN and/or AST $\geq 3 \times$ ULN) will be summarized by treatment group and by relationship of ALT or AST elevation to study medication. The percentages will be calculated relative to the number of participants with at least 1 adjudicated case. The numerator will be the number of participants with at least 1 adjudicated case in the specific category of relationship. If a participant has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Participants with an adjudicated case (i.e. ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study medication, and confounding factor(s). Additional listings will be provided for participants who meet ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively. A listing of urine pregnancy test results will be provided for female participants of child-bearing potential with at least one positive result.

11.3 Vital Signs

Descriptive statistics for vital signs (systolic and diastolic blood pressures [sitting and standing], pulse rate [sitting and standing], respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate) values at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group. Orthostatic vital sign values (orthostatic systolic and diastolic blood pressures, and orthostatic pulse rate) are defined as the corresponding standing measurement minus sitting measurement of systolic and diastolic blood pressures and pulse rate respectively.

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that will be detailed in [Table 11–3](#). The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated by treatment group. For criteria related with systolic blood pressure, diastolic blood pressure, pulse rate and weight, the denominator will be the number of participants who have available baseline and at least 1 postbaseline assessment. For criteria related with orthostatic measures, the denominator will be the number of participants who have available non-PCS baseline and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value during the study. A supportive listing of participants with PCS postbaseline values will be provided. In addition, a tabular display

showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

Table 11–3 Criteria for Potentially Clinically Significant Vital Signs

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of $\geq 7\%$
	Low	—	Decrease of $\geq 7\%$
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP = Systolic blood pressure, DBP = Diastolic blood pressure, bpm = beats per minute.

11.4 Electrocardiograms

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in [Table 11-4](#). The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

AddTableTitle
Table 11-4 Criteria for Potentially Clinically Significant Electrocardiograms

Parameter	Unit	Criterion
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTc (QTcB or QTcF) interval	msec	> 500
QTc (QTcB or QTcF) interval	msec	Increase from baseline > 60

QTc = QT interval corrected for heart rate.

QTcB = QT interval corrected for heart rate using the Bazett formula.

QTcF = QT interval corrected for heart rate using the Fridericia formula.

To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF > 450 msec, > 480 msec, and > 500 msec will be tabulated by treatment group.

The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of double-blind treatment period in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant. A tabular display of participants with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

11.5 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Population. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the participant's lifetime history, in the past 6 months, in the double-blind treatment period, and in the follow-up period will also be presented by treatment group.

Supportive listings will be provided and will include the PID number, study center number, treatment group, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.

12 Health Outcome Analyses

Health outcomes which are planned to be reported in CSR main body are provided in Section 10.4. Other health outcome analyses are documented in health economics and outcomes research SAP.

13 Subgroup Analyses

Subgroup analysis based on prior exposure (yes/no) to a migraine prevention medication with proven efficacy will be performed for the following efficacy endpoints

- Change from baseline in mean monthly migraine days across the 12-week treatment period
- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- $\geq 50\%$ reduction in 3-month average of monthly migraine days
- $\geq 75\%$ reduction in 3-month average of monthly migraine days
- 100% reduction in 3-month average of monthly migraine days

Subgroup analyses for primary efficacy endpoint based on demographic factors (age, sex, race) will be provided in the integrated summary of efficacy to facilitate the comparison across pivotal studies.

14 Interim Analysis

No interim analysis is planned.

15 Determination of Sample Size

A total sample size of 218 participants will be randomized per treatment group and that will provide at least 98% power to detect the treatment difference between each of the 3 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. The sample size of this study was selected to provide sufficient power for the primary efficacy endpoint and first 3 secondary endpoints as shown in [Table 15–1](#). The power calculations are performed by using nQuery Advisor 7.0 and based on the following assumptions:

- 1) The treatment difference from placebo will be similar to the average value across the migraine prevention studies for atogepant (Phase 2/3 Study CGP-MD-01), telcagepant ([Ho 2014](#)) and monoclonal antibodies ([Dodick 2014a](#); [Dodick 2014b](#); [Bigal 2015](#)). The standard deviation of each endpoint was estimated from an internal study that randomized approximately 800 participants. In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is assumed -1.5 days, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions are listed in [Table 15–1](#).
- 2) The study statistical testing plan controls the overall type 1 error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.0167 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.0167 (2-sided), the secondary endpoints will be tested sequentially.

Table 15–1 Statistical Power for Primary and the First Three Secondary Endpoints

Hypothesis Testing	Endpoint	Treatment Difference from Placebo	Standard Deviation	Statistical Power
Primary	Change from baseline in mean monthly migraine days across the 12-week treatment period	-1.5	3.5 ^a	98%
Secondary 1	Change from baseline in mean monthly headache days across the 12-week treatment period	-1.5	3.8 ^a	95% ^b
Secondary 2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	-1.2	3.2 ^a	93% ^b
Secondary 3	Proportion of participants with at least a 50% reduction in mean monthly migraine days across the 12-week treatment period	33% Placebo rate	50% Atogepant rate	89% ^b

^a Standard deviations observed in an internal study that randomized approximately 800 participants

^b Statistical power for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence for the comparisons of each dose versus placebo.



Allergan [REDACTED]

SAP 3101-301-002 AGN-241689

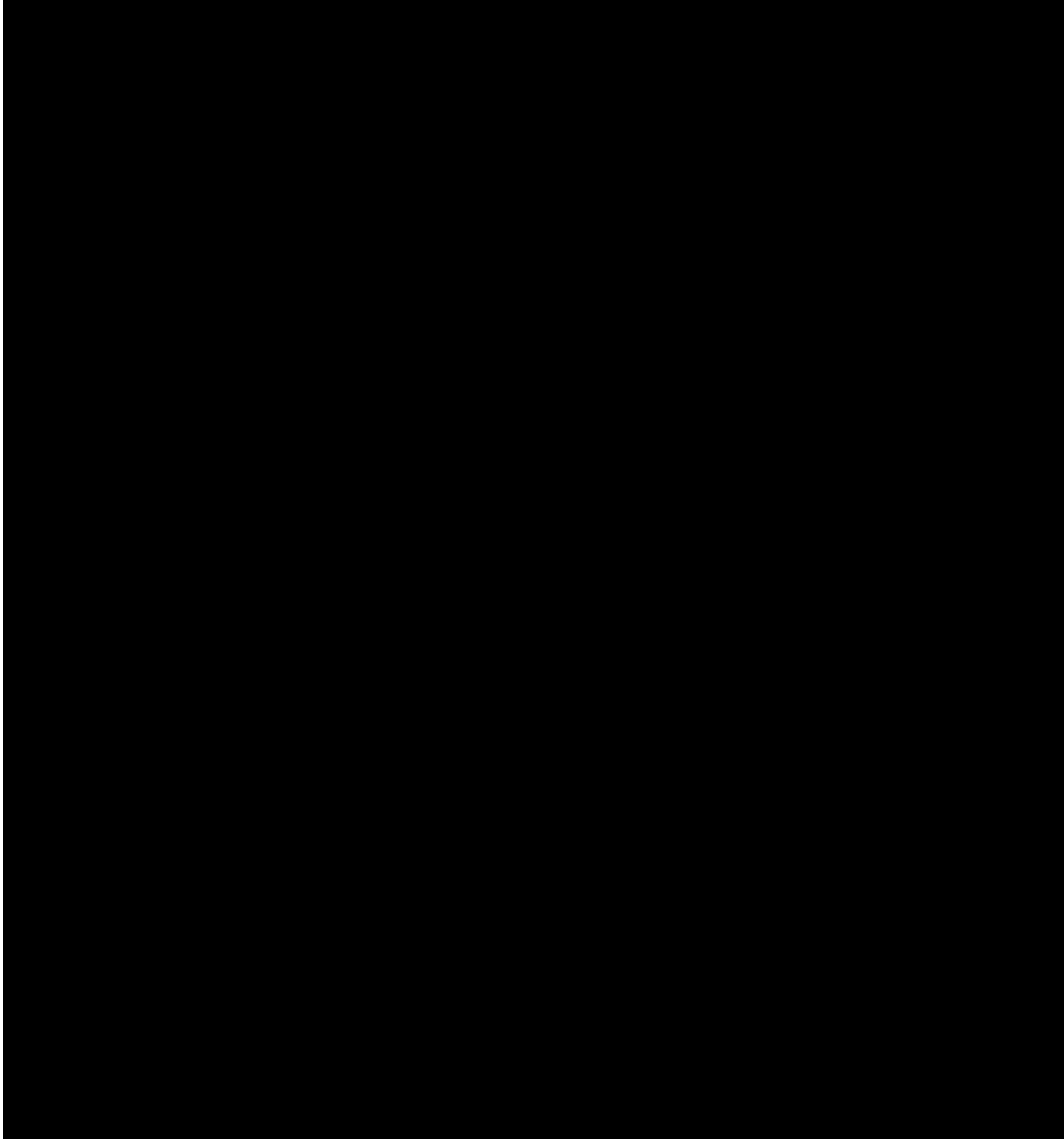
16 Statistical Software

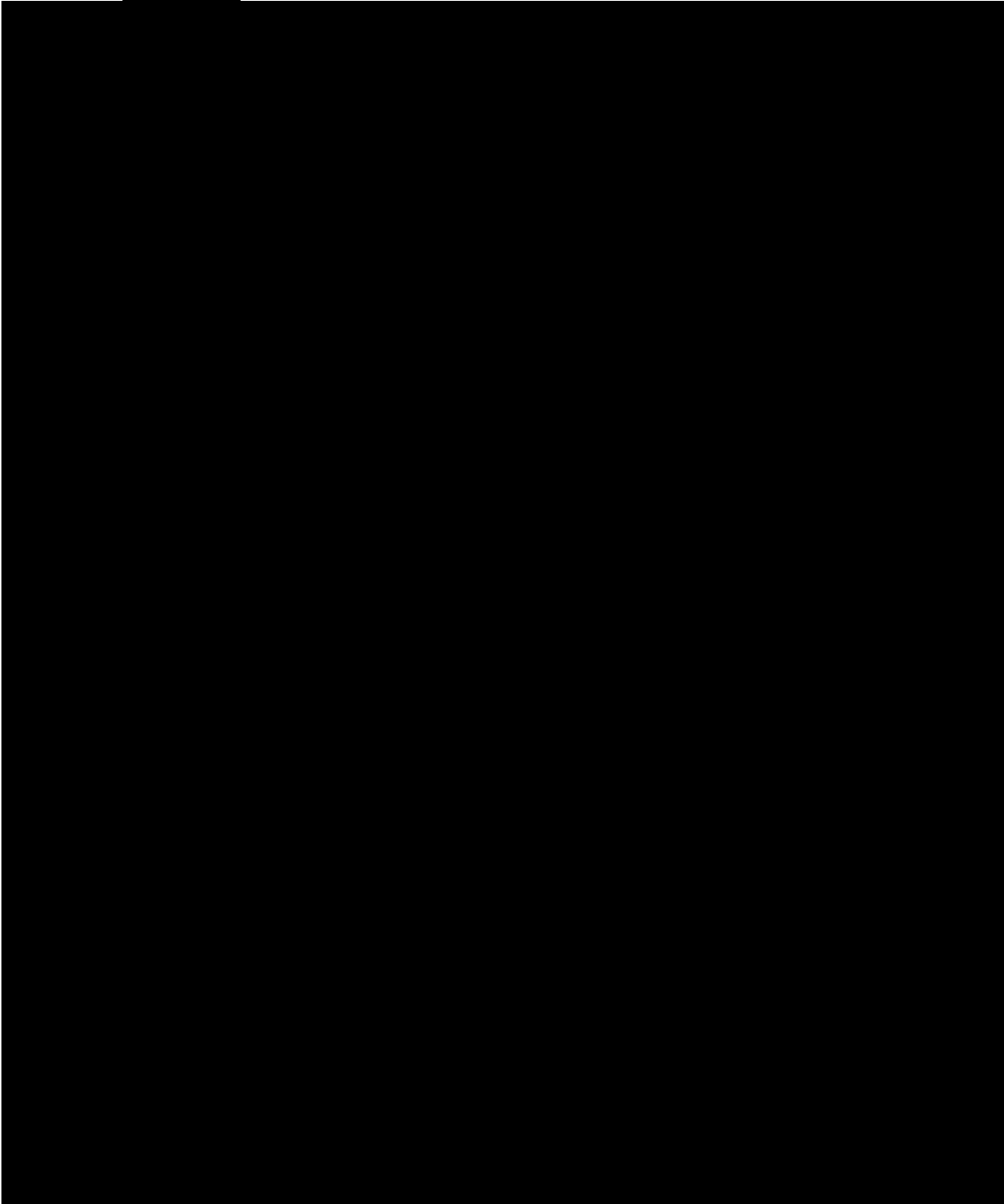
Statistical analyses will be performed using [REDACTED] SAS.

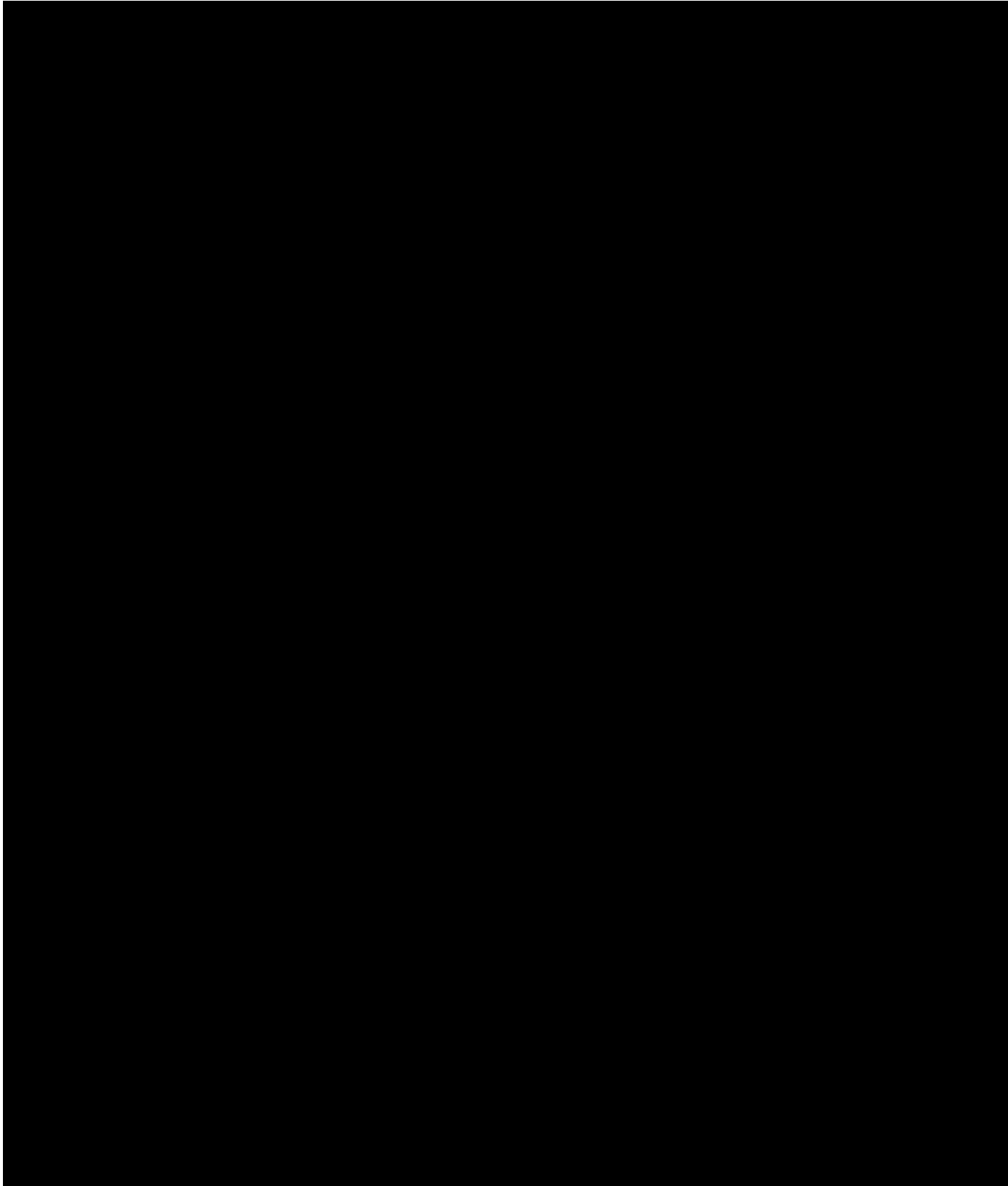
17 Data Handling Convention

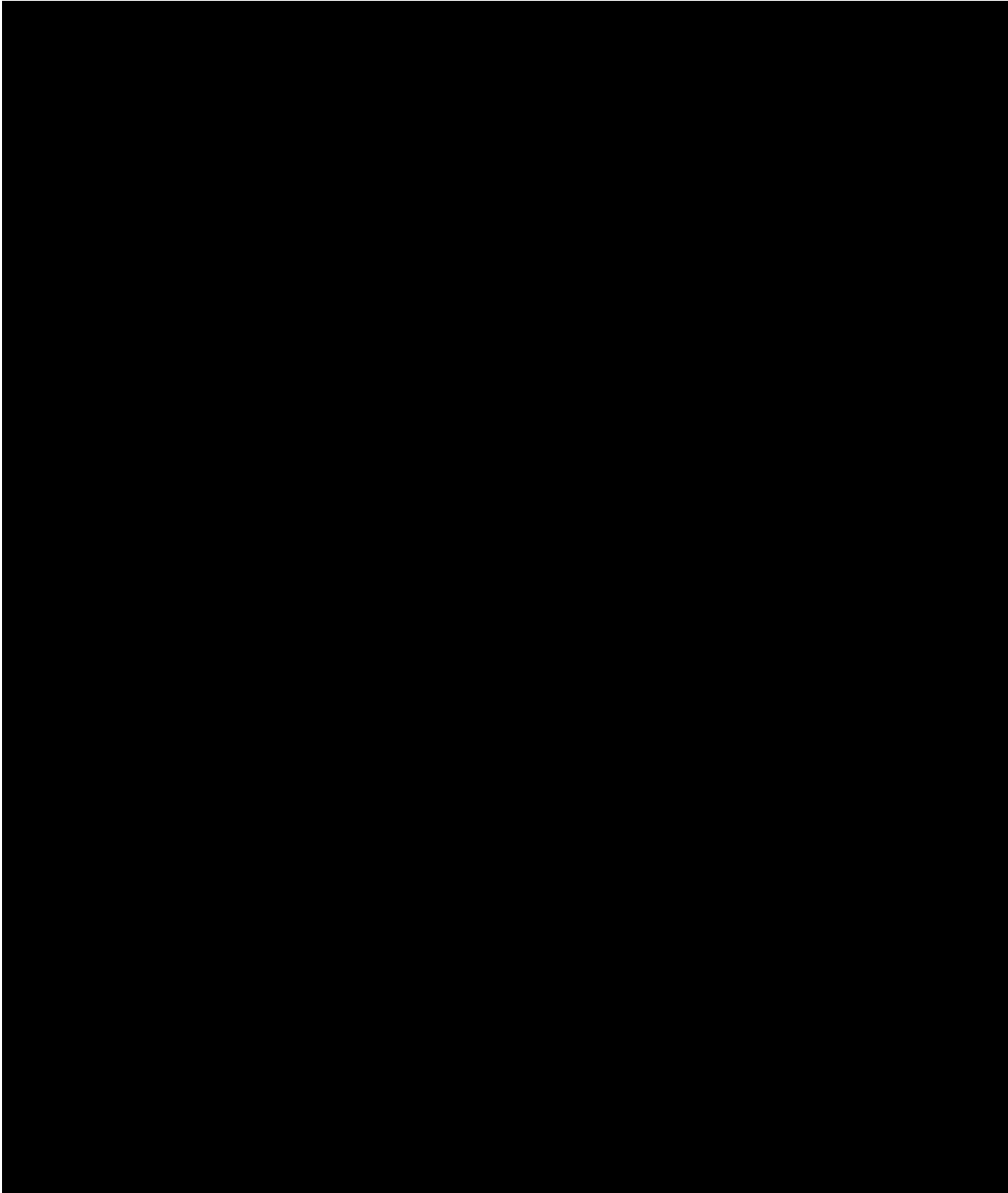
17.1 Visit Time windows

For analysis purposes, Day 1 is defined on the date of the first dose of double-blind study intervention. On-treatment Period is defined to from the first dose till the last dose.





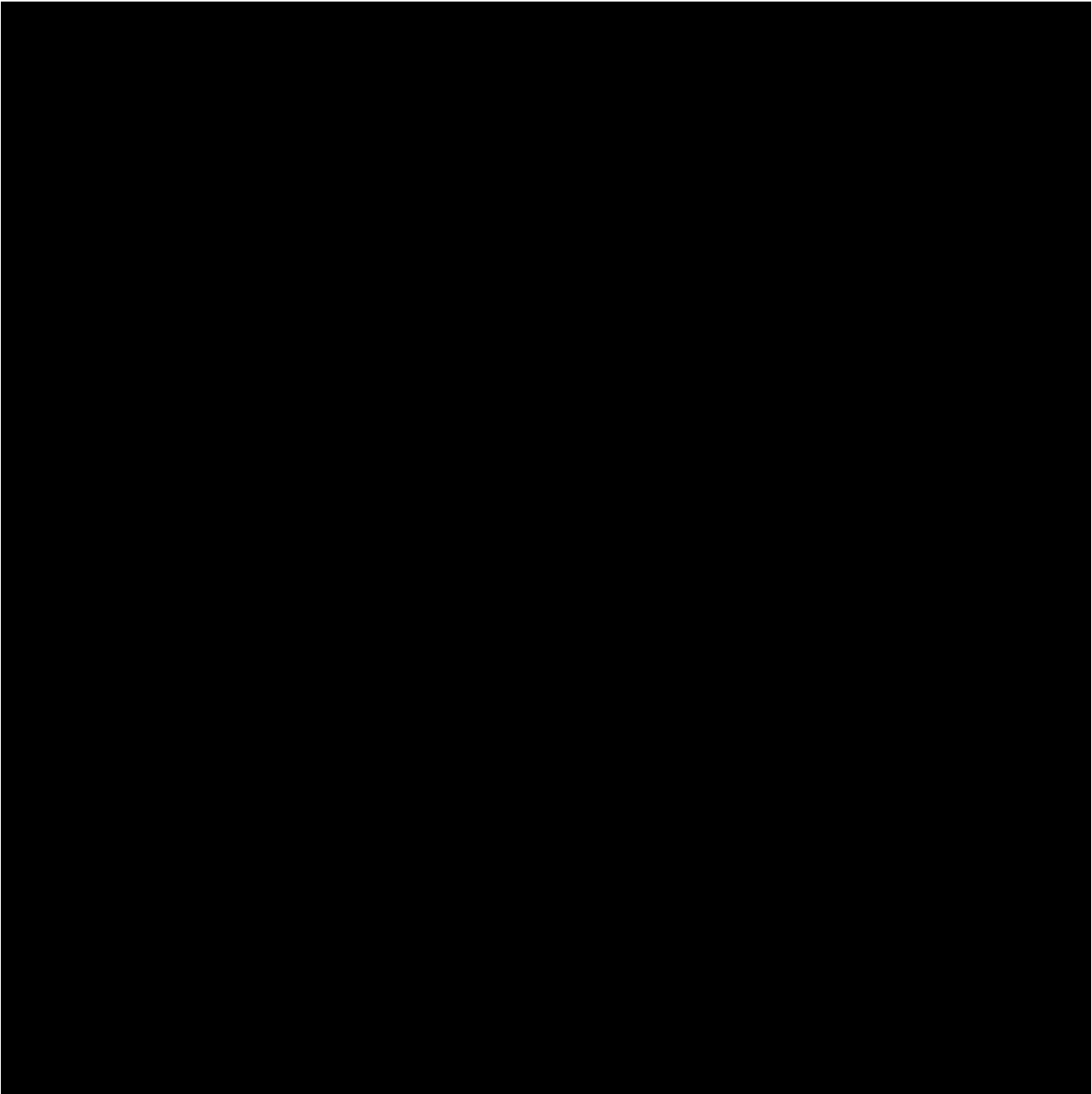


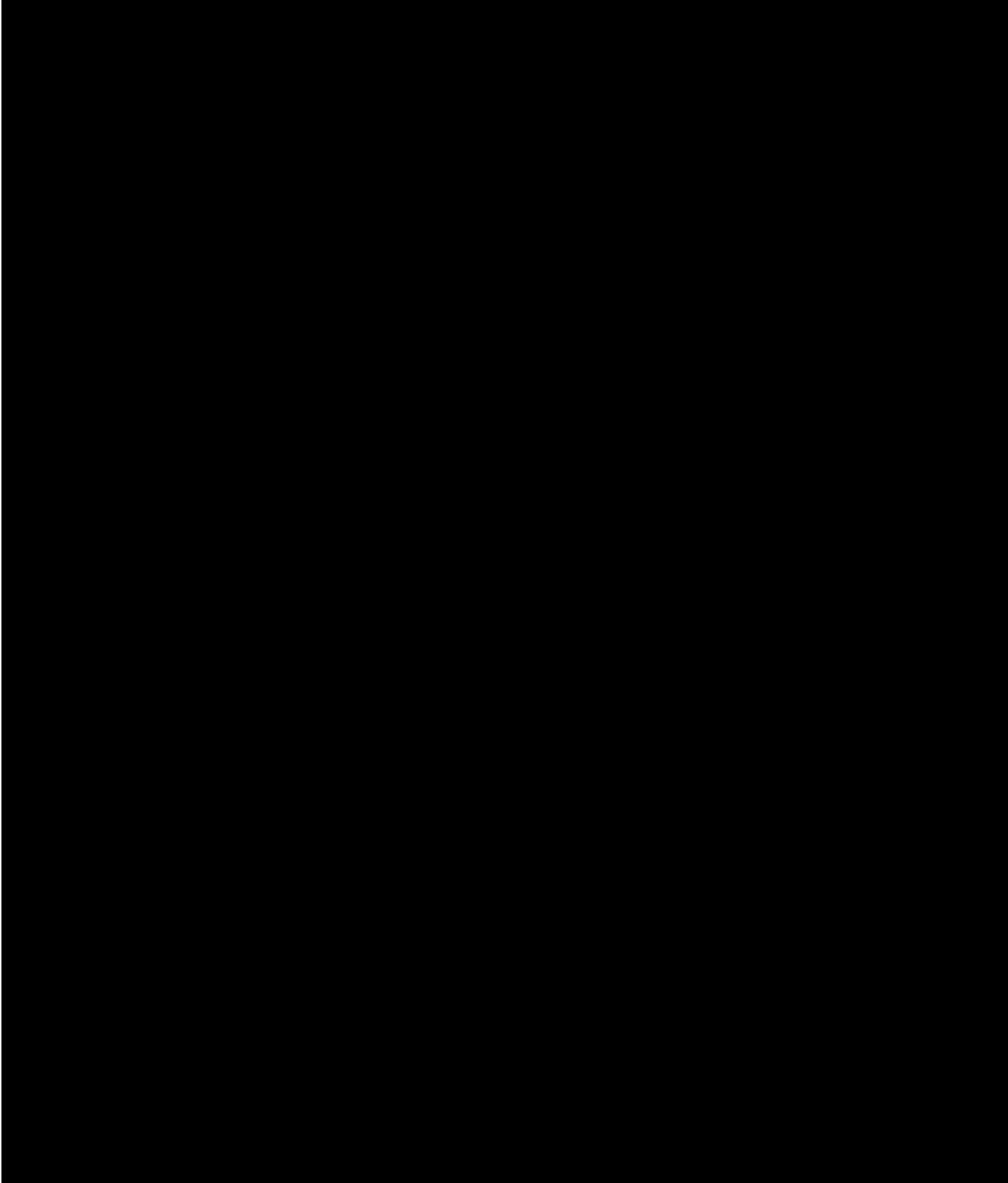


17.2 Derived Efficacy and Health Outcome endpoints

17.2.1 Derivation of Efficacy Endpoints Based on eDiary Data

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 4-week baseline period and throughout the double-blind treatment period, participants are to record eDiary information on the duration of headache, headache specific characteristics and symptoms, the pain severity, and use of any acute headache pain medication. [REDACTED]





17.2.2 Derivation of Health Outcome Endpoints

If a participant reported multiple records on the same day and records are inconsistent, then the records on the date with discrepancy will be excluded from endpoint derivation and thus excluded from the analyses. The corresponding records will be flagged in the analysis datasets.

AIM-D Related Endpoints Derivation

As described in SAP Section 10.1.2 (copied from protocol Section 6.2.1), the AIM-D was developed as a daily eDiary with a recall period 24 hours. By design, it is collected in the today diary only. The scoring of the following endpoints is completed in 2 steps.

- Monthly Performance of Daily Activities domain score of the AIM-D
- Monthly Physical Impairment domain score of the AIM -D
- Monthly AIM -D total score

Step 1: Calculate AIM-D daily domain score and total score

Daily performance of daily activities score will be calculated based on the summation of items 1-5 and 10 and 11, ranging from 0-35. A daily performance of daily activities domain score will be calculated if 4 or more item scores have non-missing responses. When the response category “I did not have <errands, leisure or social, strenuous activities> planned” (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding performance of daily activities domain score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 7, provided that 4 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (35).

Daily physical impairment scores will be calculated based on the summation of items 6-9, ranging from 0-20. A daily physical Impairment score will be calculated if 2 or more item scores have non-missing responses. The corresponding physical Impairment score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 4, provided that 2 or more item scores are available; otherwise it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (20).

A daily total score will be calculated based on the summation of items 1-11, ranging from 0-55. A Total Score will be calculated if 6 or more items scores have non-missing responses. When the response category “I did not have <errands, leisure or social, strenuous activities> planned” (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Total

Score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 11, provided that 6 or more item scores are available; otherwise it will be set to missing. The raw score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (55).

Step 2: Calculate Monthly Scores and Baseline Score

Monthly scores will be calculated using the average daily scores only if there are at least 14 non-missing daily scores in the corresponding monthly (28-day) period. The corresponding monthly scores will be calculated by summing the non-missing daily domain scores and dividing by the number of non-missing daily domain, provided that 14 or more daily scores are available; otherwise it will be set to missing.

Monthly activity level score will be calculated by summing the non-missing daily scores and dividing by the number of these scores, provided that 14 or more daily scores are available in the corresponding monthly (28-day) period; otherwise it will be set to missing. Same rule will be applied to the calculation of monthly activity limitation score.

MSQ Related Endpoints Derivation

MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps.

Step 1: Final item value assignment.

Precoded item values and final item values for each MSQ item response are shown in [Table 17–12](#).

Table 17–12 Item Values for MSQ Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Step 2: Computation of raw domain(dimension) scores

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function Restrictive domain includes Items 1 - 7, Role Function Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain.

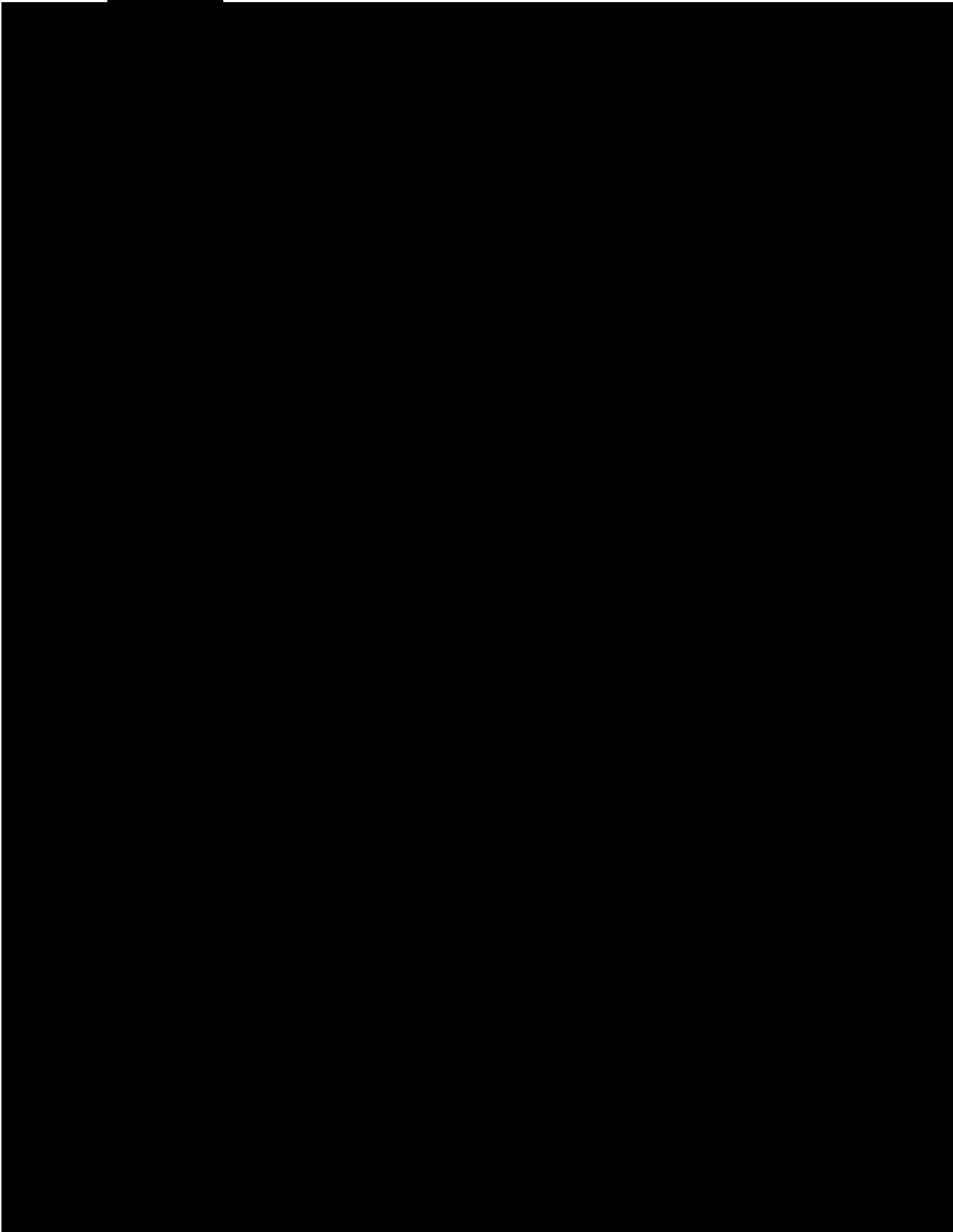
Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated using the average of the other completed items within the same dimension.

In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing.

Step 3: Linear transformation to a 0 to 100 scale.

The transformation formula for each MSQ 2.1 domain are listed below

- Role Function -Restrictive: $\frac{(raw\ score-7)*100}{35}$
- Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$
- Emotional Function: $\frac{(raw\ score-3)*100}{15}$



17.3 Repeated or Unscheduled Assessments of Safety Parameters

Baseline is defined as the last assessment made before the first dose of double-blind study treatment. If a participant has 2 or more visits within the same window, the last visit with a non-missing value will be used for summary over time unless specified otherwise. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

17.4 Missing Date of the Last Dose of Study treatment

When the date of the last dose of the double-blind study treatment is missing, all efforts should be made to obtain the date from the Investigator. If it is still missing after all efforts have been made, the last available study medication date will be used in the calculation of treatment duration.

17.5 Missing Severity Assessment for Adverse Events

If severity is missing for an AE that started before the date of the first dose of double-blind study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of double-blind study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.6 Missing Causal Relationship to Study treatment for Adverse Events

If the causal relationship to the double-blind study treatment is missing for an AE that started on or after the date of the first dose of double-blind study treatment, a causality of yes will be assigned. The imputed values for causal relationship to double-blind treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

17.7 Missing Date Information for Adverse Events

The following imputation rules only apply to cases in which the start date for AEs is incomplete (i.e., partly missing).

17.7.1 Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study treatment, the month and day of the first dose of double-blind study treatment will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the first dose of double-blind study treatment, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of double-blind study treatment, *January 1* will be assigned to the missing fields

17.7.2 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.7.3 Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study treatment, the day of the first dose of double-blind study treatment will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study treatment, the last day of the month will be assigned to the missing day
- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of double-blind study treatment, the date of the first dose of double-blind study treatment will be assigned to the missing start date
- If the stop date is before the date of the first dose of double-blind study treatment, the stop date will be assigned to the missing start date

17.8 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

17.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

17.8.2 Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of double-blind study treatment, the month and day of the first dose of double-blind study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of double-blind study treatment, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the first dose of double-blind study treatment, *January 1* will be assigned to the missing fields

17.8.3 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.8.4 Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of double-blind study treatment, the day of the first dose of double-blind study treatment will be assigned to the missing day
- If either the year of the incomplete start date is before the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of double-blind study treatment, the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of double-blind study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of double-blind study treatment, the first day of the month will be assigned to the missing day

17.8.5 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, replace it with the last visit date in the imputations described below. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

17.8.6 Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

17.8.7 Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

17.8.8 Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day
- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day
- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

17.9 Character Values of Clinical Laboratory Parameters

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

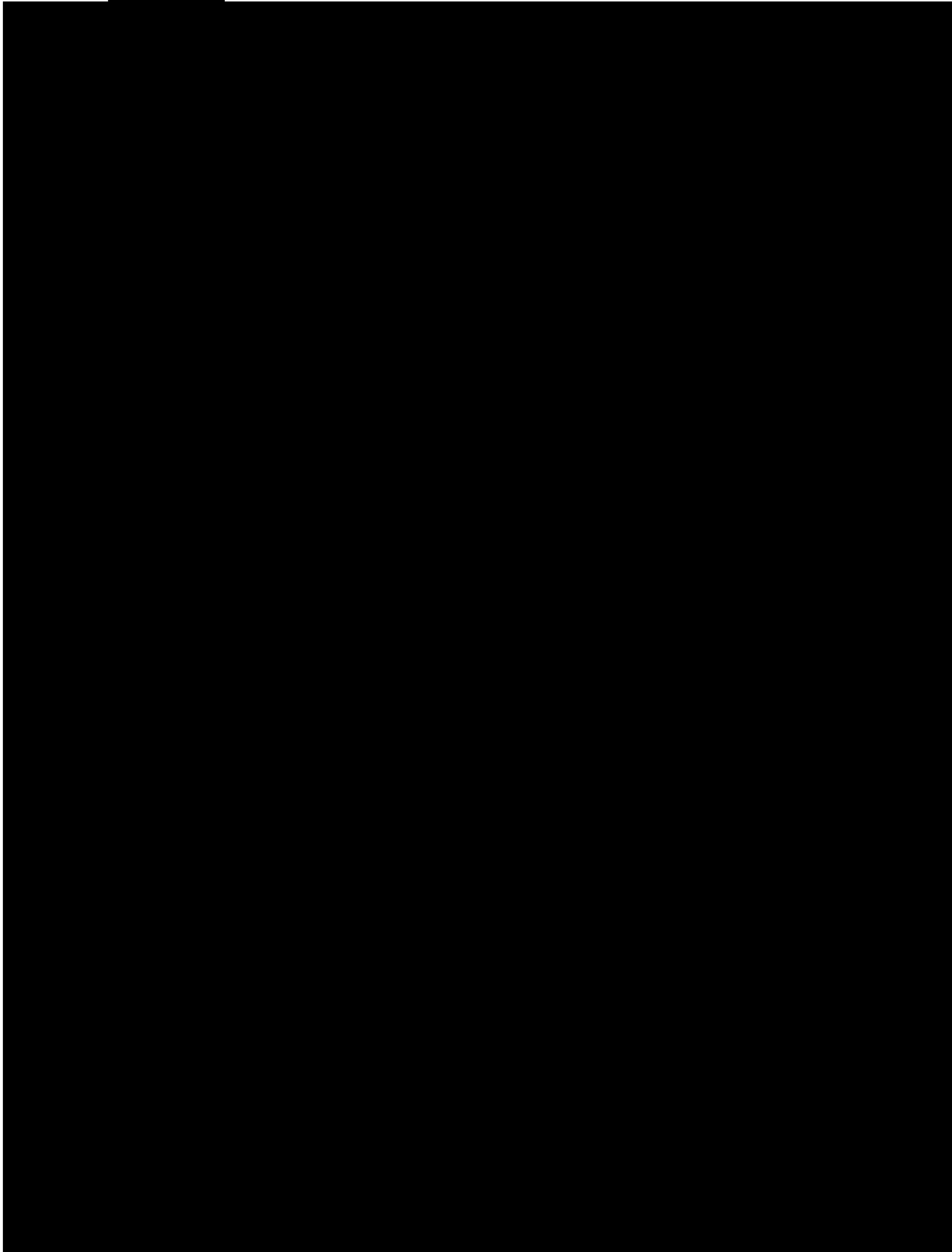
17.10 Identifying Prior Exposure (yes/no) to a Migraine Prevention**Medications with Proven Efficacy Based on Prior Medications Reported in eCRF**

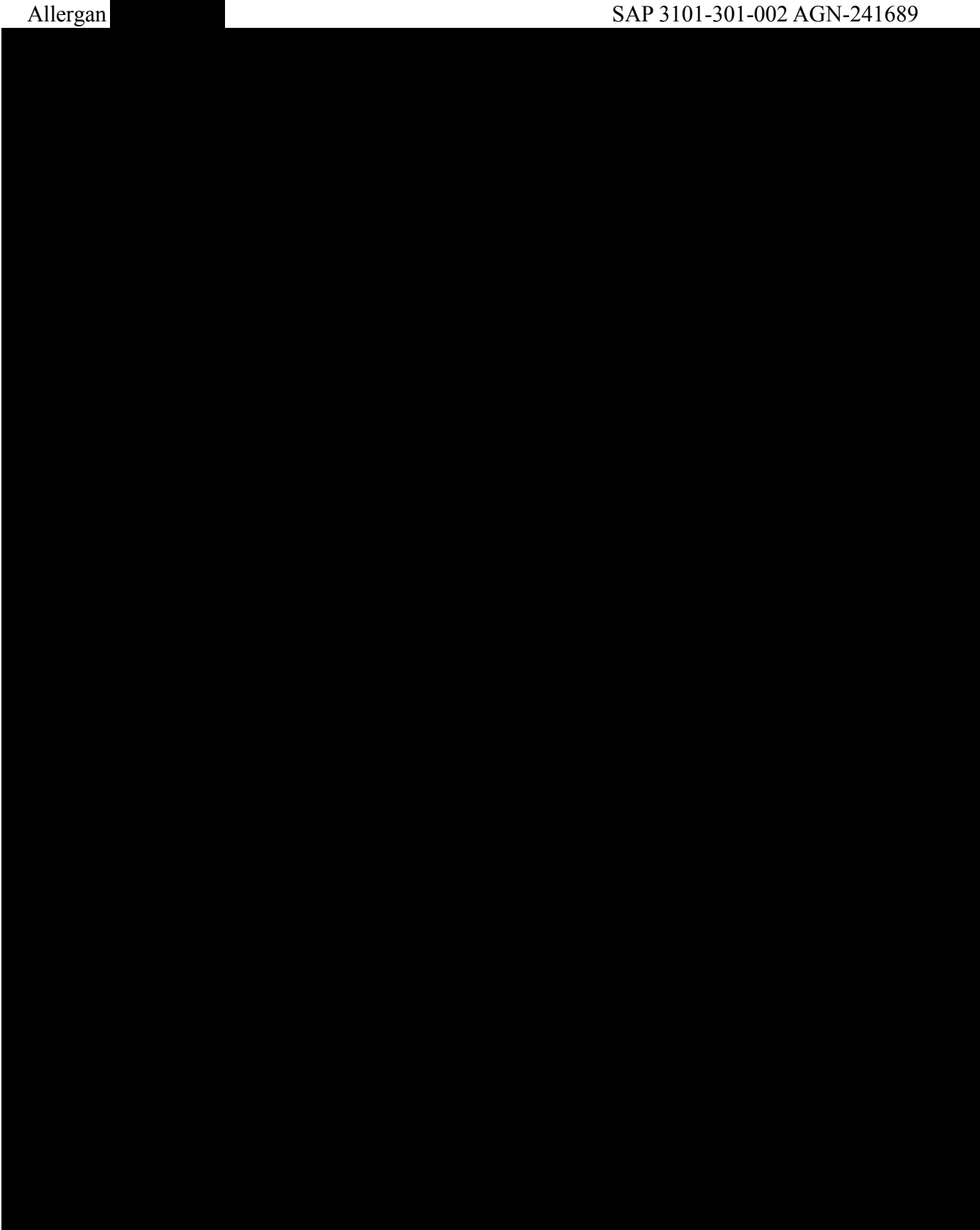
According to Appendix 12.3.1 in the protocol, a list of migraine-preventive medications with proven efficacy was identified by clinical team and coding team as shown in [Table 17–14](#).

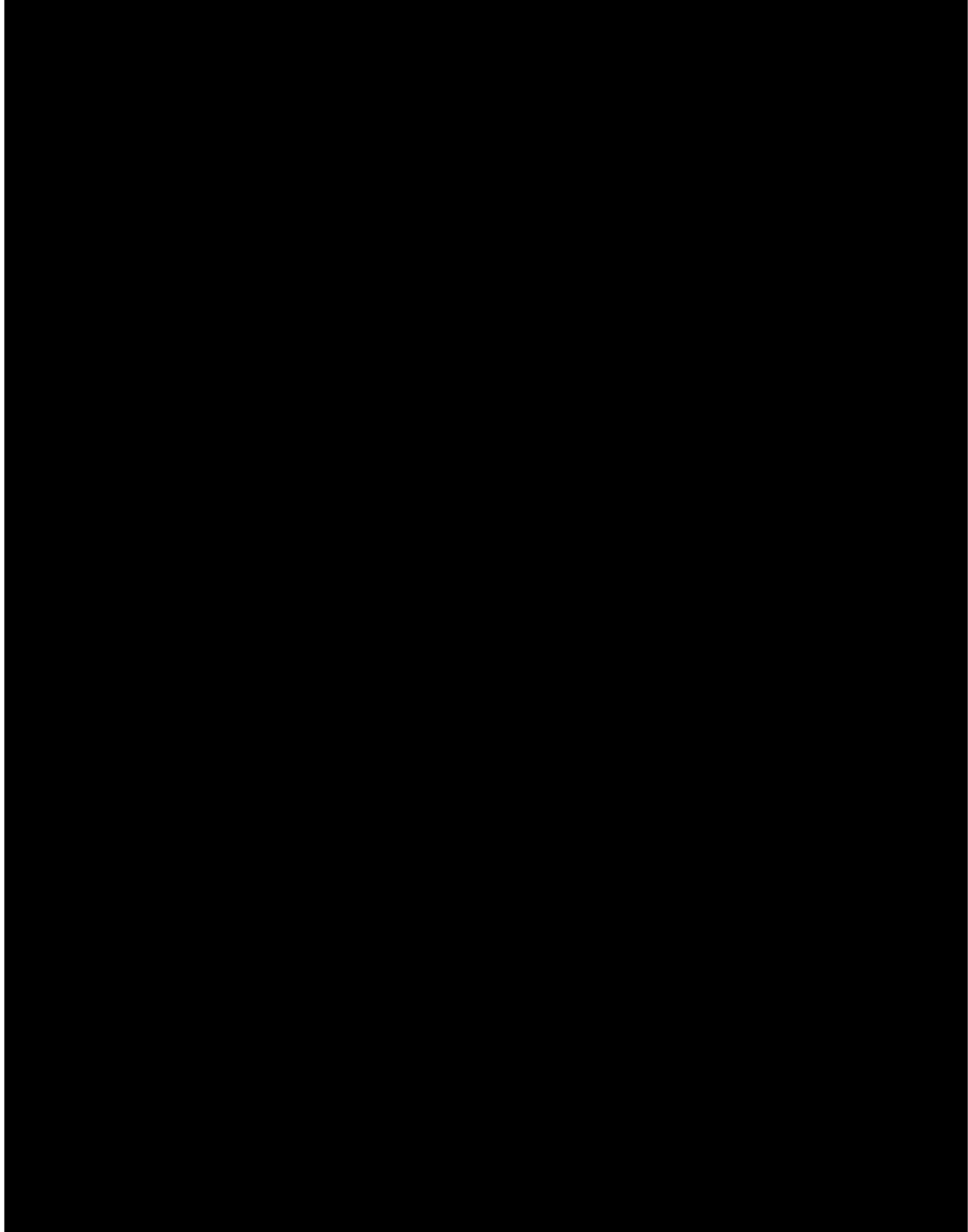
If a participant has taken medications before the screening visit with preferred names in [Table 17–14](#), and the prior medications are classified as “Migraine Prevention Medication” in the prior and concomitant medications eCRF, then the prior exposure to migraine prevention medications with proven efficacy will be “Yes” for this participant, otherwise, it is set as “No.”

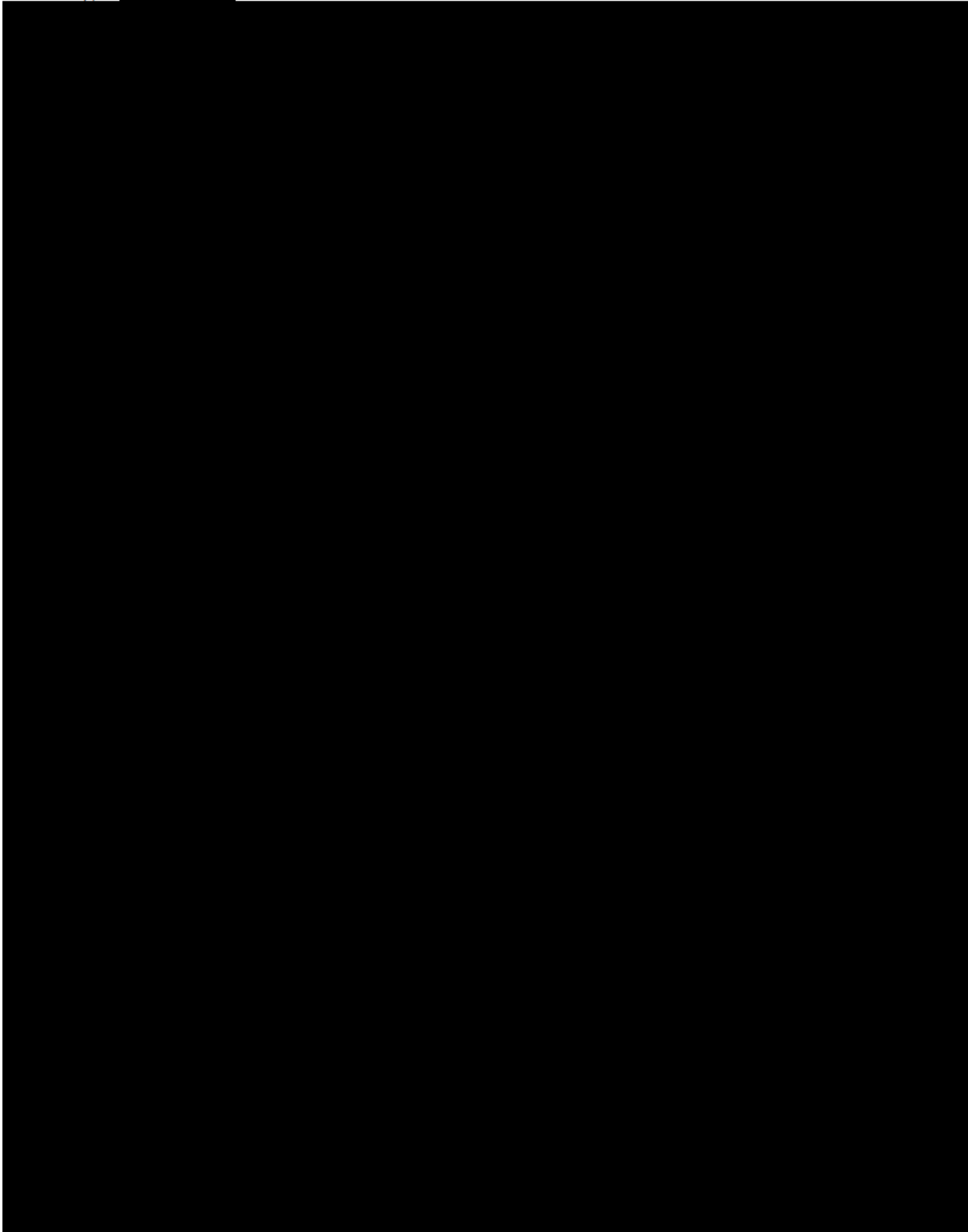
Table 17-14 List of Migraine-preventive Medications with Proven Efficacy

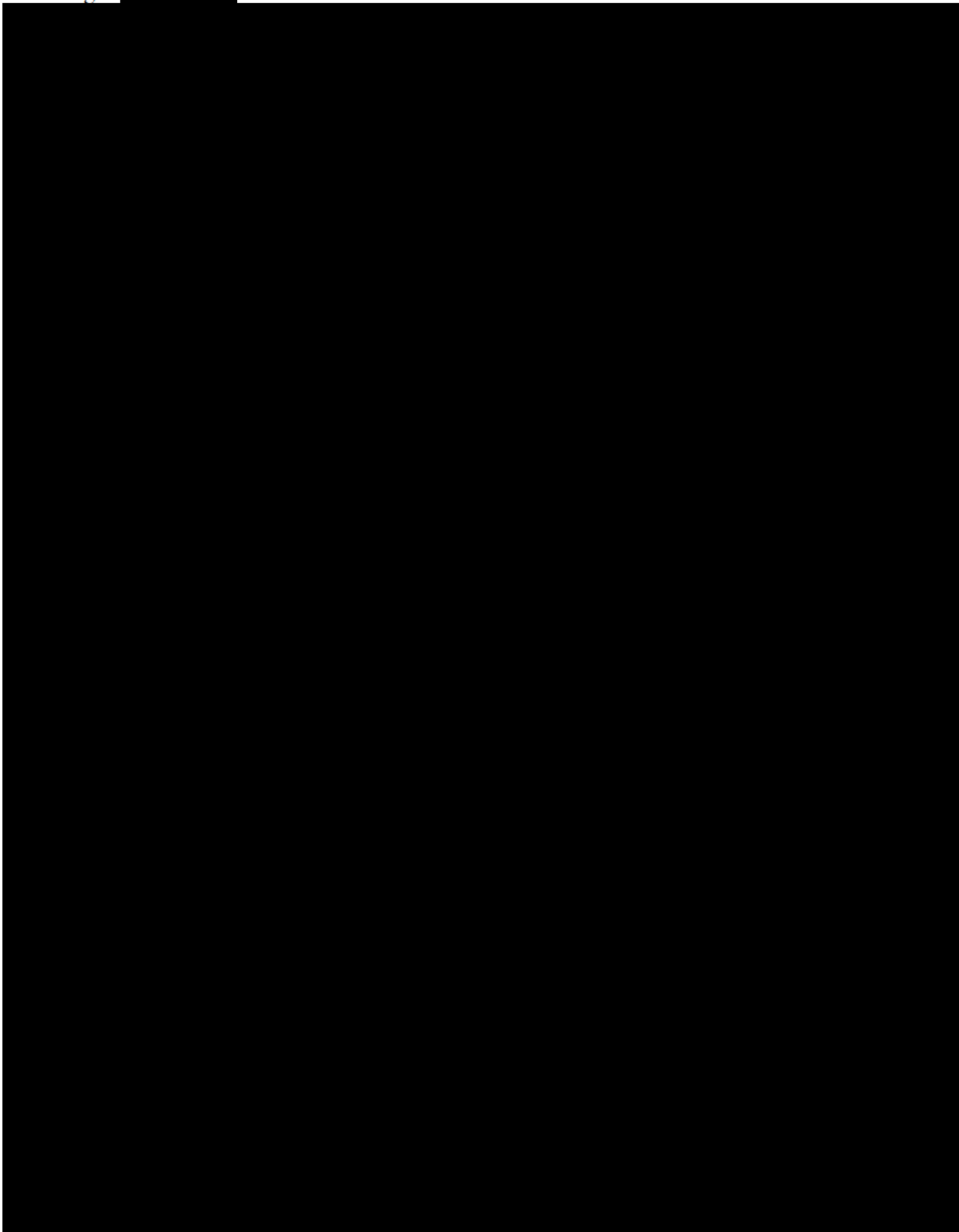
[REDACTED]

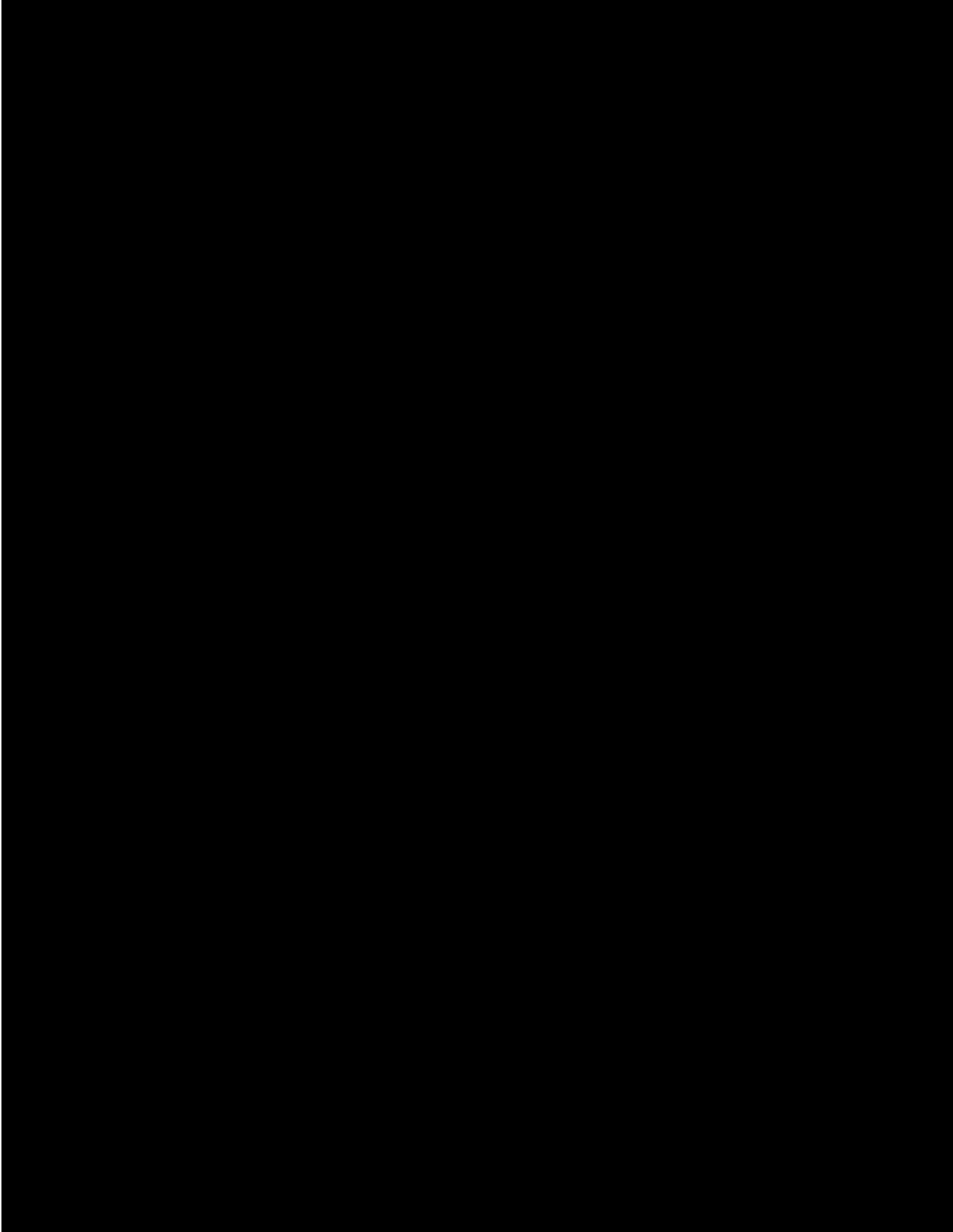


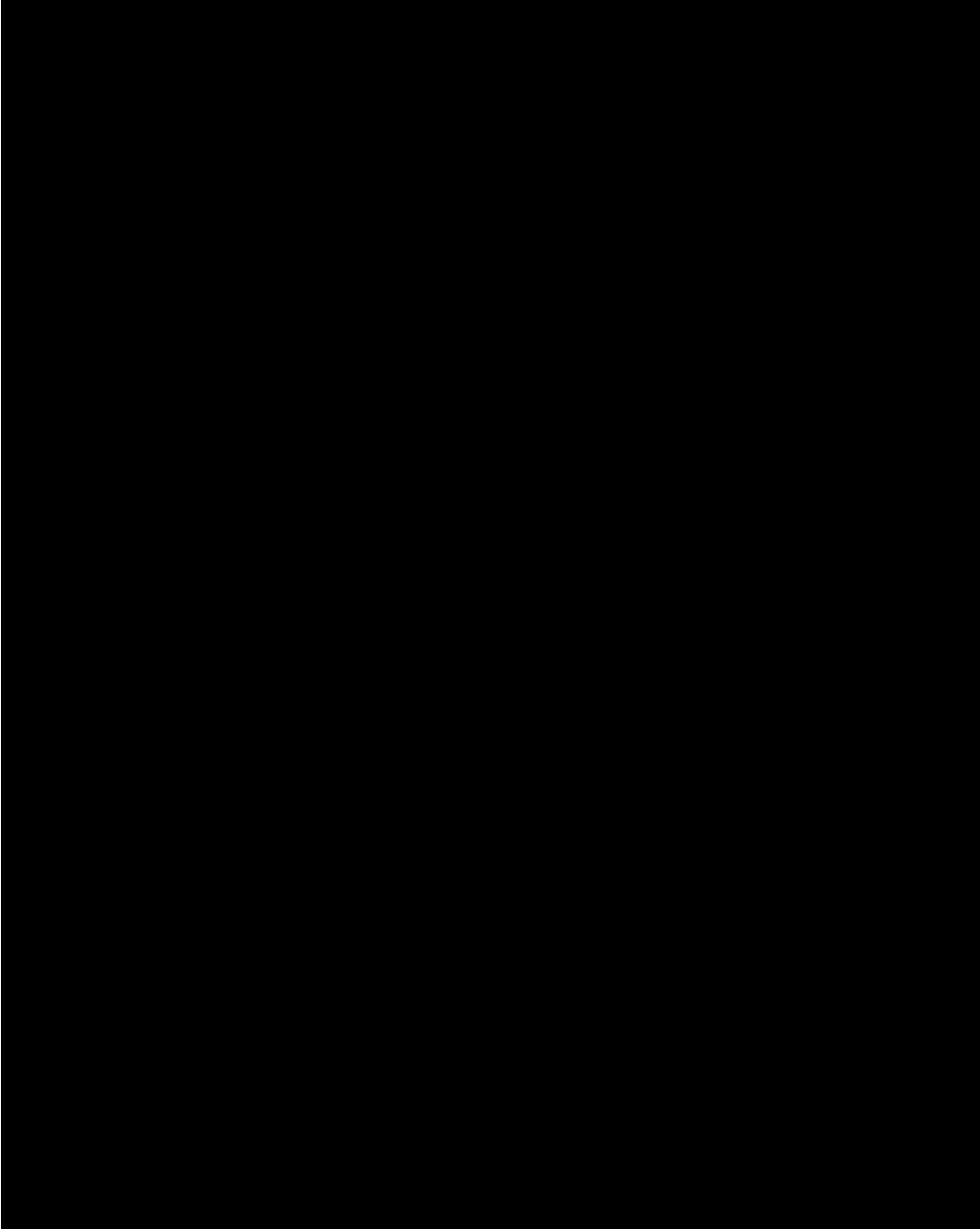


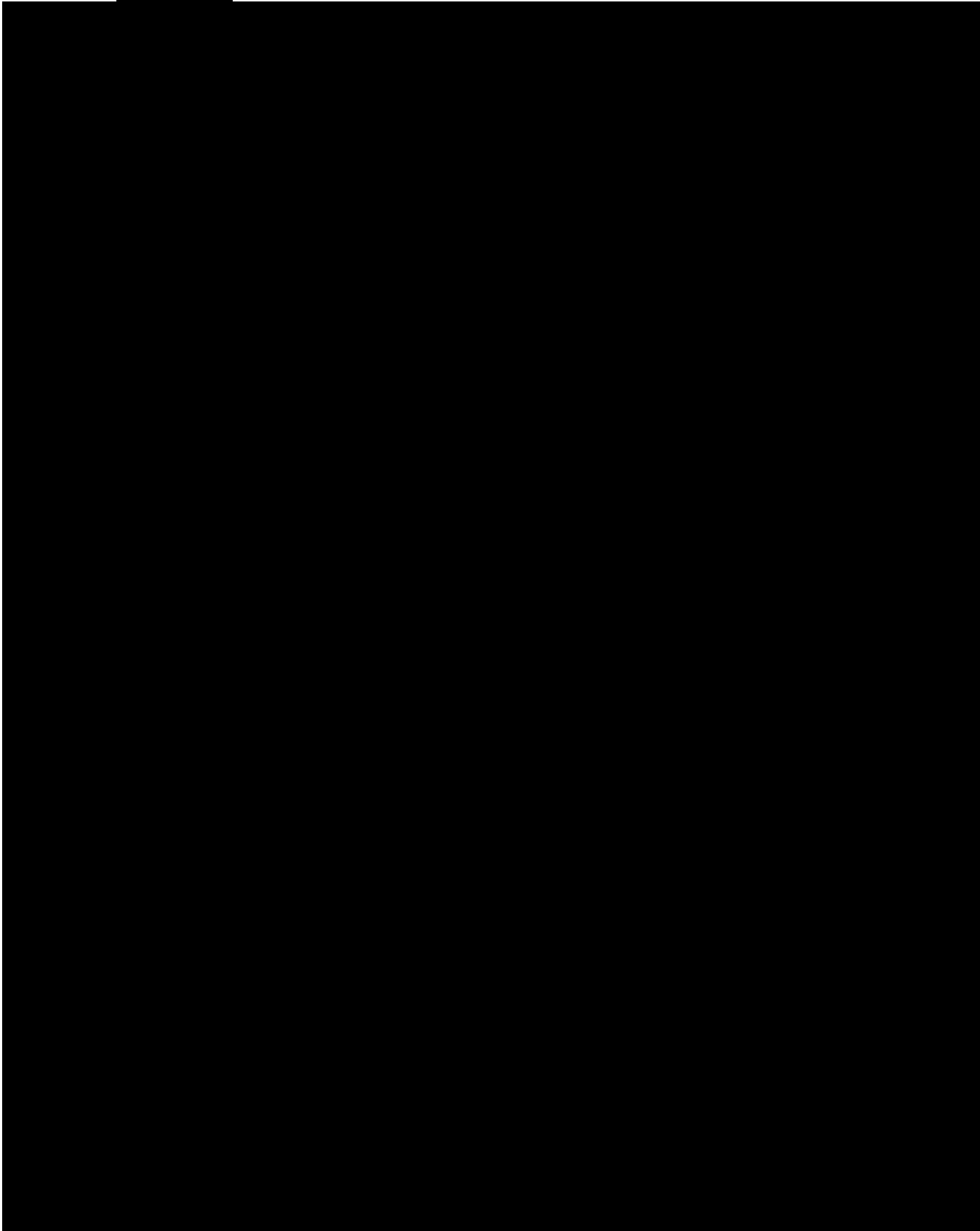












17.11 Identifying Participants Who Took a New Migraine Prophylaxis Treatment with Proven Efficacy Based on Concomitant Medications Reported in eCRF for the Intercurrent Events Specified in the Off-Treatment Hypothetical Estimand

To identify the participants who started a new migraine prophylaxis treatment as specified in Section 10.5.4 (Accounting of Intercurrent Events), the following criteria are used:
A participant has taken prophylaxis medications during the double-blind or follow-up period with preferred names in the Table 17-14, and the concomitant medications are classified as “Migraine Prevention Medication” in concomitant medications eCRF.

18 COVID-19 Related Analyses

To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol clarification letter and corresponding protocol amendment were sent to sites during the pandemic to allow remote visits (as described in the protocol Table 2 Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic).

This section specifies analyses for evaluating the impact of COVID-19.

18.1 Efficacy Evaluation

Efficacy Endpoints

Table 18–1 describes the collection devices for primary and key secondary endpoints. The primary endpoint and 5 key secondary endpoints are collected via eDiary according to protocol design. Minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses every day.

The endpoint, MSQ v2.1 Role Function Restrictive domain score at Week 12, will be collected using eTablet as one electronic patient reported outcome (ePRO) at site. The remote collection for this endpoint was in production starting from April 20,2020. Participants are required to complete the ePRO measures remotely at Visit 7 (Week 12) according to remote-visit procedure (Table 4–2).

To evaluate the missing rate for this endpoint at Week 12, the number of participants who missed at least one ePRO assessment due to COVID-19 will be summarized at each visit in the mITT Population (efficacy analyses population).

Table 18–1 Summary of Collection Devices for Primary and Key secondary endpoints

Hypothesis Testing	Node	Endpoint	Collection device
Primary	P1	Change from baseline in mean monthly migraine days across the 12-week treatment period	eDiary
Secondary 1	S1	Change from baseline in mean monthly headache days across the 12-week treatment period	eDiary
Secondary 2	S2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	eDiary
Secondary 3	S3	≥ 50% reduction in 3-month average of monthly migraine days	eDiary
Secondary 4	S4	Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12	eTablet
Secondary 5	S5	Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period.	eDiary
Secondary 6	S6	Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period.	eDiary

Power and Sample Size Evaluation

The study achieved the last participants first visit on January 31, 2020. A total of 910 patients were randomized, and the number of randomized participants exceeded the planned sample size 872. It is expected the missing rate during the pandemic might be slightly higher than the missing rate before the pandemic. No big impact for the power and sample size calculation is anticipated.

18.2 Safety and other evaluations

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visit (missing entire visit due to COVID-19 or missing assessments due to COVID-19)
- Protocol deviation
- Study drug disruption due to COVID-19
- TEAEs related with COVID-19

Safety Population will be used for the planned analyses described above. The number of participants impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of participants impacted by COVID-19 and their corresponding disposition status in the double-blind treatment period and the follow-up period will be summarized respectively.

The number of participants who missed at least one entire visit due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of participants who missed

at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit.

The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug disruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to corona virus infection or coronavirus test positive will be provided.

Supporting listings for the described analyses above will be provided.



Allergan [REDACTED]

SAP 3101-301-002 AGN-241689

19 Changes to Analyses Specified in Protocol

None.

20 References

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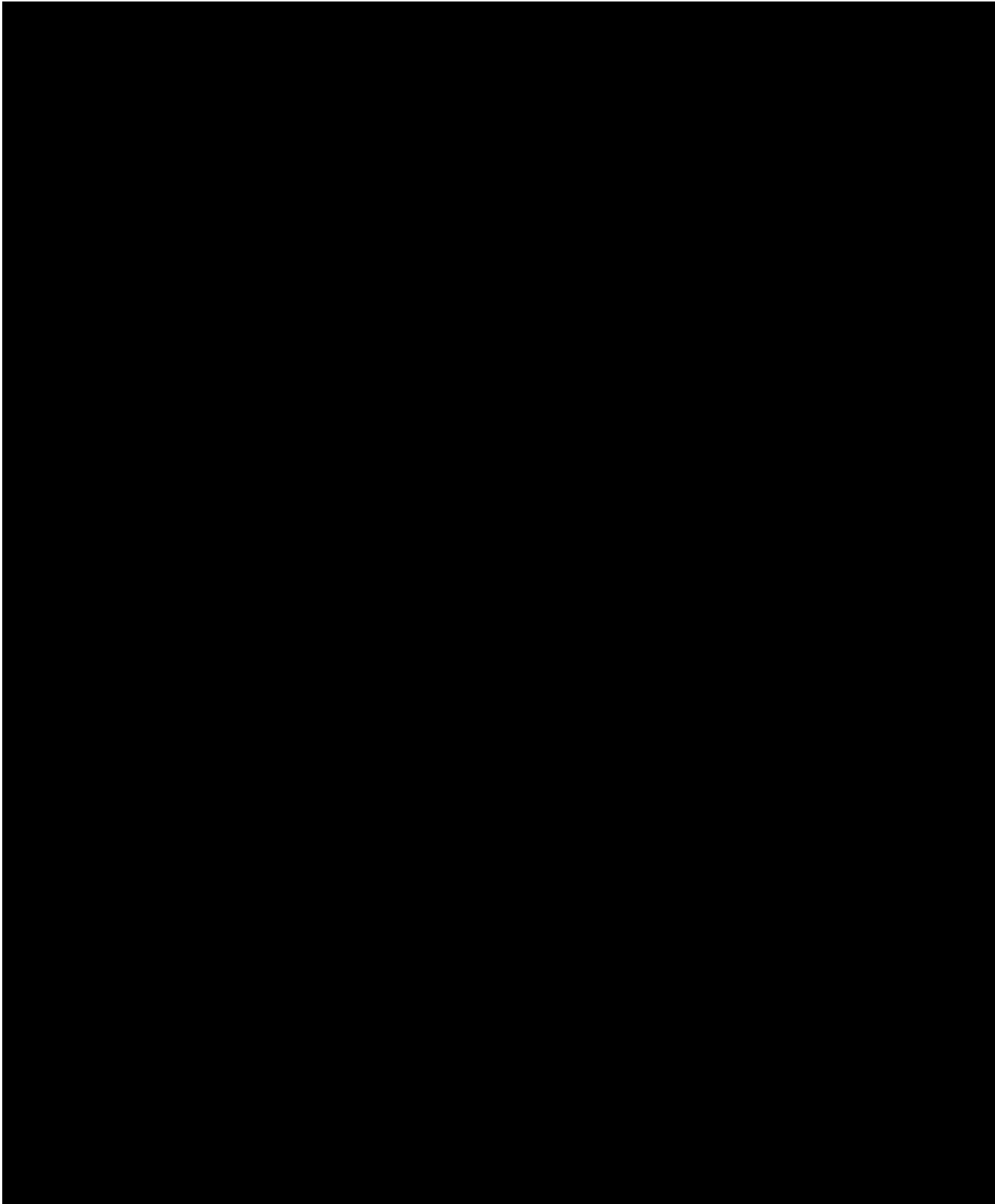
Ho TW, Connor KM, Zhang Y, Pearlman E, Koppenhaver J, Fan X, Lines C, Edvinsson L, Goadsby PJ, Michelson D. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*. 2014 Sep 9;83(11):958-66.

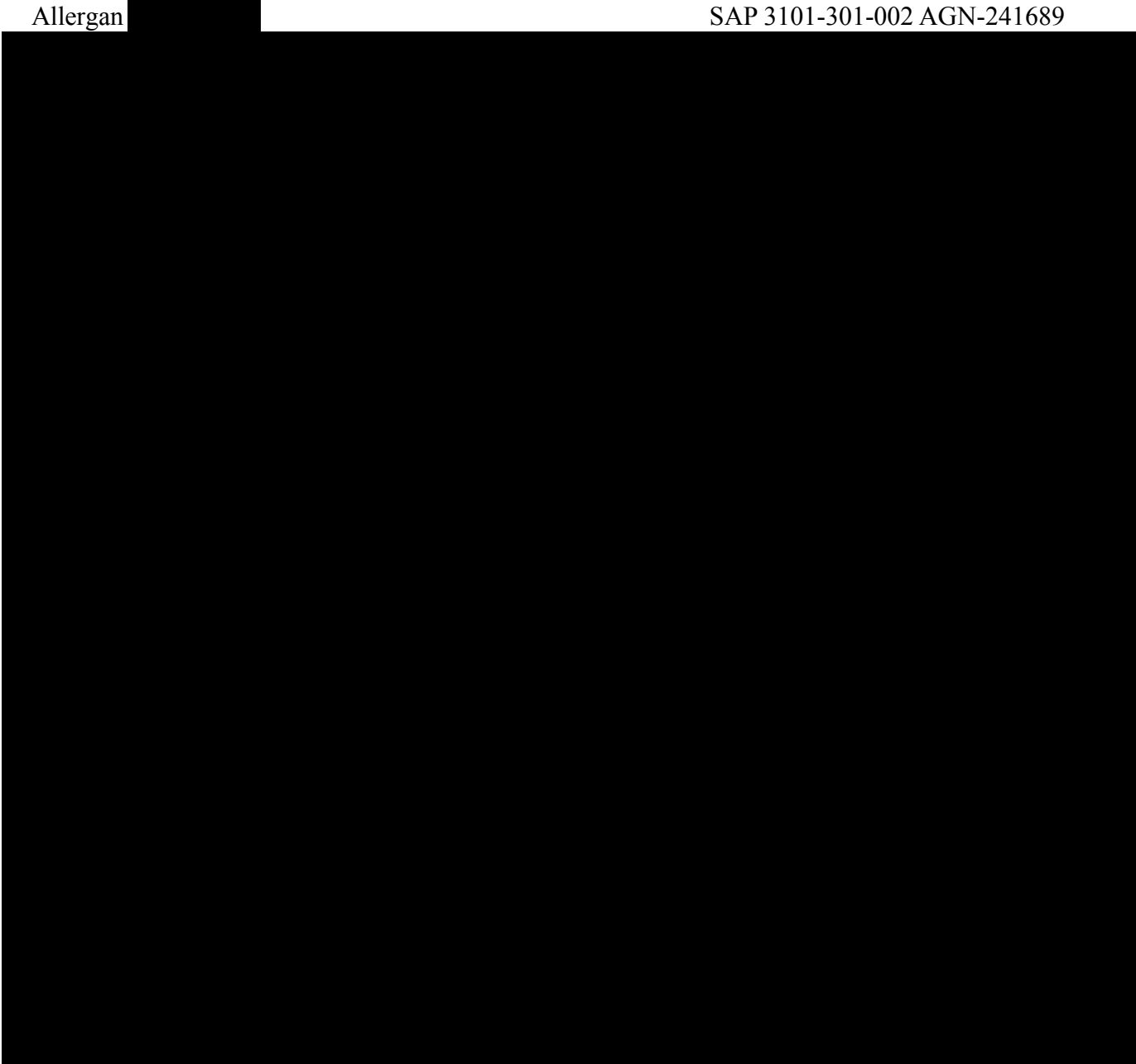
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Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. *Biometrics*. 2012 Dec;68(4):1250-9.

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys*. New York, NY: Wiley.

**APPENDIX I. REPORTING SELECTED LABORATORY PARAMETERS IN
CONVENTIONAL UNIT**





Electronic Signatures

User	Date	Justification
[REDACTED]	29-Jun-2020 14:23:57 (GMT)	Subject Matter Expert Approval
[REDACTED]	26-Jun-2020 14:03:15 (GMT)	Document Originator Approval
[REDACTED]	26-Jun-2020 13:59:45 (GMT)	Manager Approval
[REDACTED]	26-Jun-2020 21:58:07 (GMT)	Manager Approval
[REDACTED]	26-Jun-2020 19:06:31 (GMT)	Document Originator Approval