NCT02867709

Study ID: UBR-MD-02

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

Statistical Analysis Plan Amendment 1 Date: 21-Mar-2018

1. Title Page

STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

Final: 2017-05-17

Amendment #1: 2018-03-21

Protocol Number:	UBR-MD-02 Amendment 3
Development Phase:	3
Product Name:	Ubrogepant
Study Statistician:	[redacted]
Sponsor:	Allergan, Inc. [redacted]

2. Table of Contents

2.1 List of Tables

[redacted]

2.2 List of Figures

[redacted]

[redacted]

3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
C-SSRS	Columbia–Suicide Severity Rating Scale
CFB	change from baseline
CHD	coronary heart disease
CSR	clinical study report
CV	cardiovascular
DBS	dry blood spot
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
EQ VAS	European Quality of Life Visual Analogue Scale
EQ-5D-5L	European Quality of Life 5 Dimensional – 5 Level
EU	European Union
FDS	Functional Disability Scale
FWER	familywise error rate
HEOR	Health Economics and Outcomes Research
HR	hazard ratio
INR	international normalized ratio
IP	investigational product
IWRS	interactive web response system
kg	kilogram(s)
KM	Kaplan-Meier
LOCF	last observation carried forward
LS	least squares
m	meter(s)
MedDRA	Medication Dictionary for Regulatory Activities
mg	milligrams
mITT	modified intent-to-treat
PCS	potentially clinically significant
PF	pain free
PGIC	Participant Global Impression of Change
[redacted]	[redacted]
PO	Primary Objective
PR	pain relief
PT	preferred term
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 ($QTcF = QT/(RR)^{1/3}$)

Abbreviation/Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation
SE	standard error
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
SPF	sustained pain freedom
SPR	sustained pain relief
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States of America
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 17May2017 of Study UBR-MD-02. Specifications of tables, figures, and data listings are contained in a separate document. [redacted]

This document is organized into 3 main sections:

1. Study overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

4.1 Study Design Summary

Structure: Multicenter, randomized, double-blind, placebo-controlled, parallel-group, single attack study; randomization to placebo, ubrogepant 25 mg, or ubrogepant 50 mg.

Duration: The study includes a screening period of up to 14 days prior to randomization, a 60-day period in which to treat a single migraine attack, and a 4-week follow-up period.

Study Treatment Groups: Ubrogepant 25 mg, ubrogepant 50 mg

Controls: Ubrogepant placebo

Dosage/Dose Regimen: Study participants will have up to 60 days to treat a single qualifying migraine attack of moderate or severe headache pain intensity at home. Participants have the option to take a second dose of investigational product (IP) or rescue medication if the participant has either a nonresponding migraine or a migraine recurrence. Participants who are randomized to ubrogepant arms will be randomly assigned at the Randomization Visit (Visit 2) to active treatment or placebo (1:1) for the blinded optional second dose. Participants randomized to the placebo arm will receive placebo for their blinded optional second dose.

Randomization/ [redacted] Participants will be randomized (1:1:1) to 1 of the following 3 treatment groups: placebo, ubrogepant 25 mg, or ubrogepant 50 mg. [redacted]

Number of Participants: Approximately 1650 participants will be randomized (550 per treatment arm).

4.2 Study Objectives and Endpoints

Each study objective is presented with corresponding endpoint(s) below:

Table 4-1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
Primary • [PO1] To compare the efficacy, safety, and tolerability of 2 doses of ubrogepant (25 and 50 mg) with placebo in participants with a single migraine attack	**Primary Efficacy Endpoints** The coprimary efficacy parameters for the United States of America (US) are as follows: • [P1] Pain freedom (PF) at 2 hours after the initial dose, defined as a reduction in headache severity from moderate/severe at baseline to no pain, at 2 hours after the initial dose • [P2] Absence of the most bothersome migraine-associated symptom (the most bothersome migraine-associated symptom will be identified at baseline for each participant) at 2 hours after the initial dose. [redacted] **Secondary Efficacy Endpoints** The secondary efficacy parameters for the US are: • [S1] Pain relief (PR) at 2 hours after the initial dose, defined as the reduction of a moderate/severe migraine headache to a mild headache or to no headache, at 2 hours after the initial dose • [S2] Sustained pain relief (SPR) from 2 to 24 hours after the initial dose, defined as pain relief with no administration of either rescue medication or the second dose of IP, and with

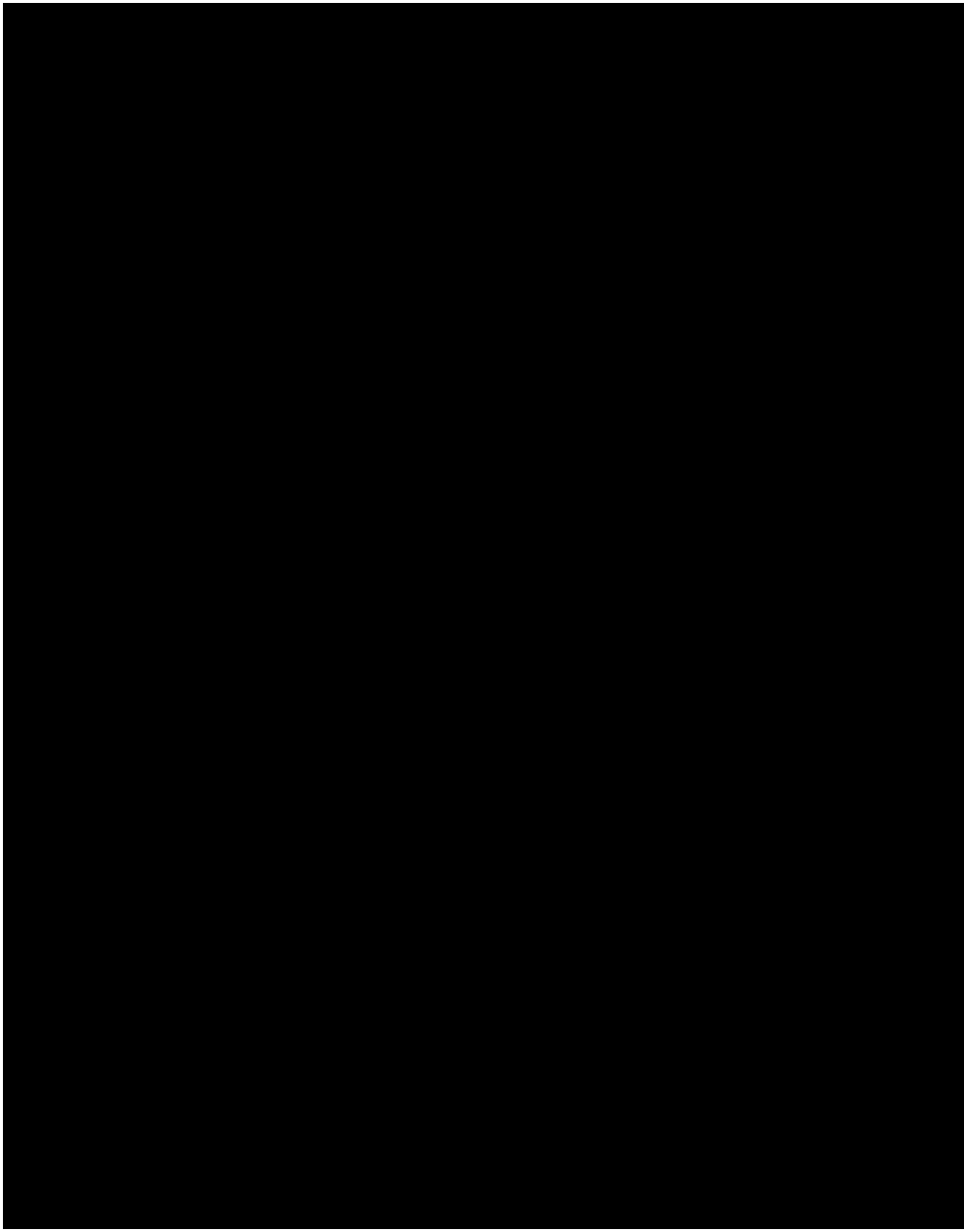
Objectives	Endpoints
	no occurrence thereafter of a moderate/severe headache during the relevant number of hours after dosing with the IP • [S3] Sustained pain freedom (SPF) from 2 to 24 hours after the initial dose, defined as pain freedom with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a mild/moderate/severe headache during the relevant number of hours after dosing with the IP • [S4a] Absence of photophobia at 2 hours after the initial dose • [S4b] Absence of phonophobia at 2 hours after the initial dose • [S4c] Absence of nausea at 2 hours after the initial dose [redacted]

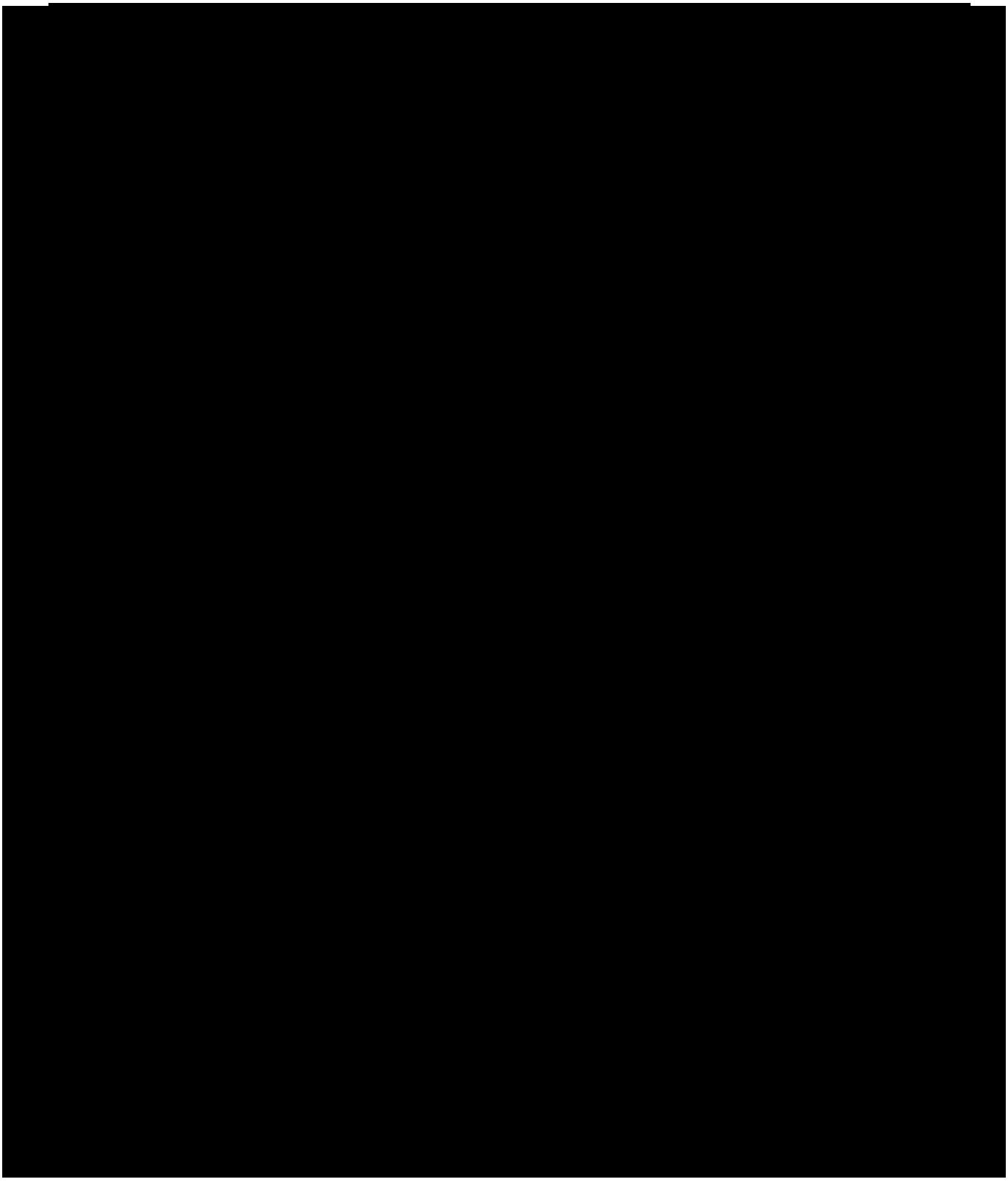
Objectives	Endpoints
	[redacted]

Objectives	Endpoints
	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

Objectives	Endpoints
	[redacted]





5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This statistical analysis plan (SAP) will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the clinical study report (CSR) report as Appendix 16.1.9.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5-1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who signed informed consent and received a participant identification (PID) number	—
Intent-to-Treat (ITT)	All randomized participants	Randomized assignment
Modified Intent-to-Treat (mITT)	All randomized participants who received at least 1 dose of study treatment, recorded a baseline migraine headache severity measurement, and had ≥ 1 post dose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint.	Randomized assignment
Safety	All participants who received ≥ 1 dose of study treatment	Actual received

5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Placebo
- Ubrogepant 25 mg
- Ubrogepant 50 mg

5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for

main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Table 5-2 Statistical Methodology

Methodology		Description
M1	Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

M2	Categorical descriptives	• Number and percentage of participants in individual categories
		  ○ Participants with ≥ 1 qualifying event counted once per individual category
		• N1 if proportion denominator ≠ number of participants in the population (standard percentage denominator)
		  ○ N1 = participants with non-missing baseline value

[redacted]		[redacted]
[redacted]		[redacted]
M5	Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = participants with non-missing value
M6	CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit
[redacted]		[redacted]

M8	Responder	• Categorical descriptives using proportions for responders and nonresponders
		  ○ Nonresponders include:
		  ▪ Participants who do not meet responder criteria
		• N1 = all participants unless otherwise specified

[redacted]		[redacted]

M10	Logistic regression model	• Measures the relationship between the binary categorical dependent variable (responder or nonresponder) and independent variables
		  ○ Independent variables for initial dose:
		  ▪ treatment group (placebo, ubrogepant 25 mg, ubrogepant 50 mg)
		  ▪ historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve)
		  ▪ use of medication for migraine prevention (yes, no)
		  ▪ baseline headache severity (moderate or severe)

Methodology	Description
	Note: Historical triptan response and use of medication for migraine prevention are stratification factors for the study. For the analysis of individual migraine-associated symptoms, baseline presence/absence of the symptom will be included as an additional covariate in the logistic regression model. [redacted] ○ If the logistic regression model fails to converge due to complete or quasi-complete separation, Firth's penalized likelihood method (Firth, 1993) will be used. The profile penalized likelihood approach (Heinze and Schemper, 2002) will be used to make valid inference. • Formal test of efficacy hypothesis comparing 2 active treatments vs Placebo conducted using pairwise contrasts based on odds ratios and their 95% confidence intervals of the odds ratio ○ Calculate two-sided p-values
[redacted]	[redacted]

CFB = change from baseline; ANCOVA = analysis of covariance.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.4 Missing Data

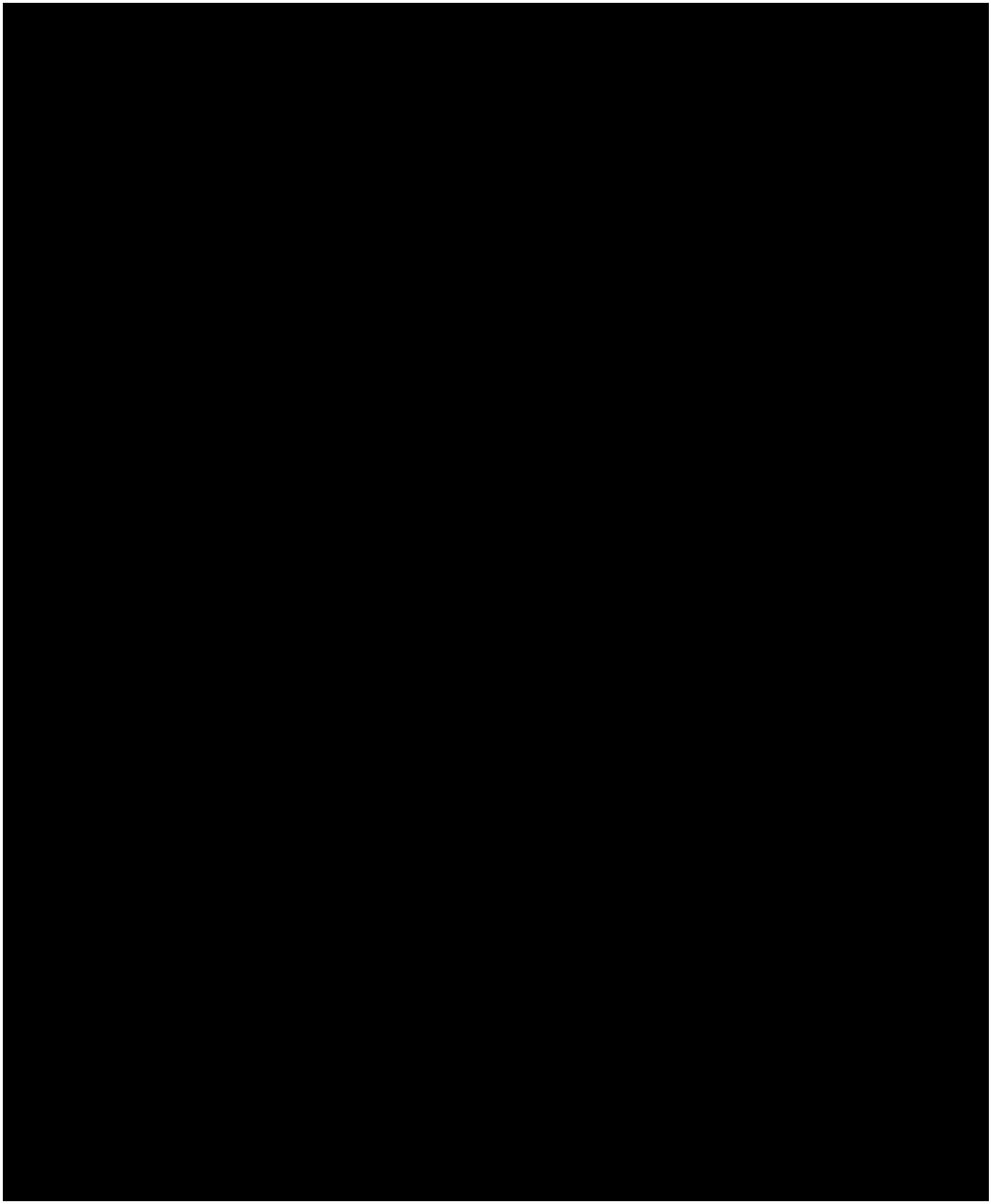
General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

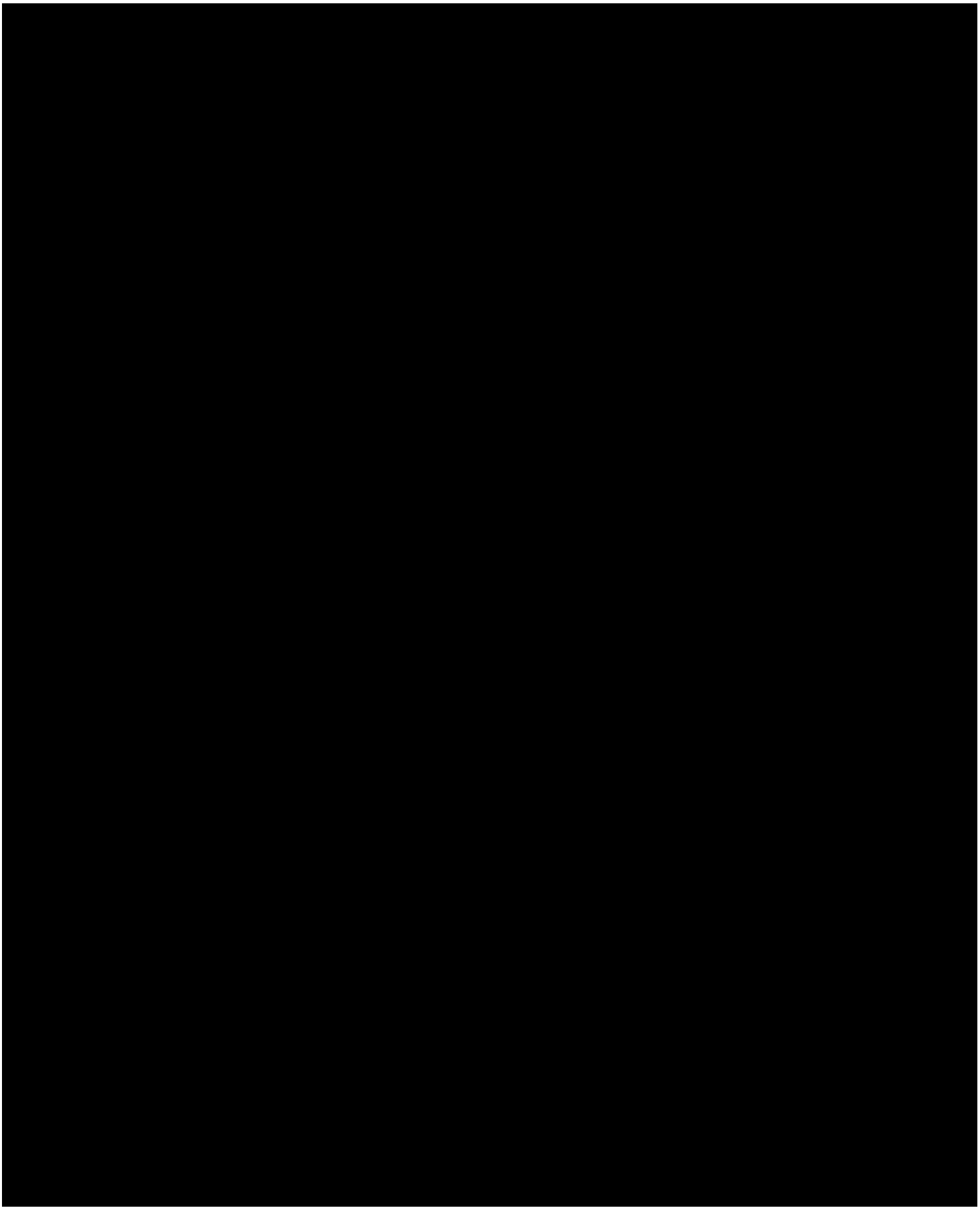
Table 5-3 Missing Data Handling by Endpoint Type

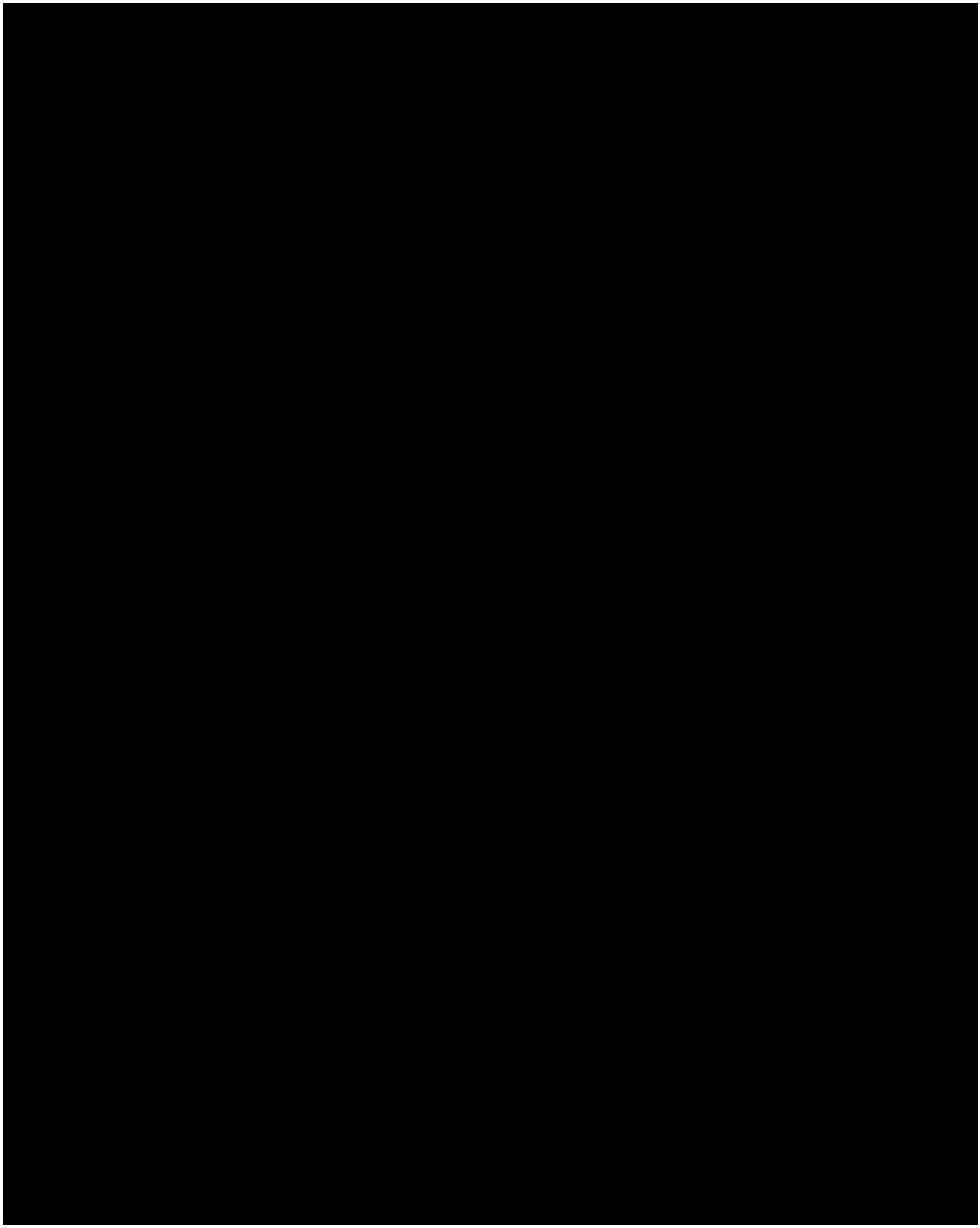
Parameter type	Timing	Missing Data Handling
[redacted]	[redacted]	[redacted]
Responder	Treatment Period	• If missing headache severity, migraine-associated symptoms, satisfaction with study medication, or functional disability scale at scheduled postdose time points, use LOCF • Sensitivity analysis for the primary efficacy endpoints is to impute participants with missing data at 2 hours as non-responders, ***provided that the participant has at least 1 postdose value before 2 hours after the initial dose***
[redacted]	[redacted]	[redacted]

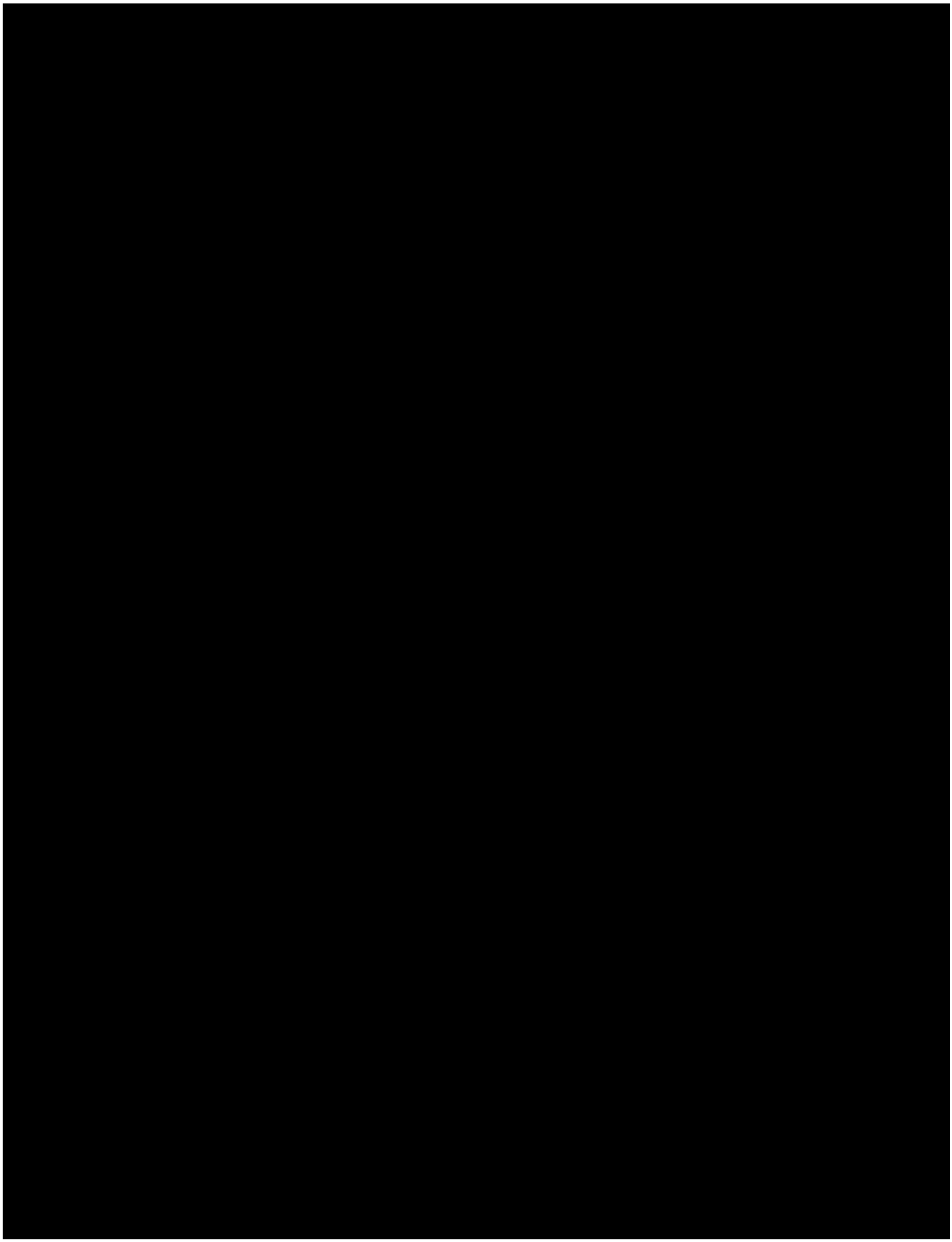
A conservative approach will used to resolve the incompatibility between the answers to the headache recurrence questions at the 24- and 48-hour time points by setting the answer to the recurrence question at the 48-hour time point the same as the answer to the recurrence question at the 24-hour time point, when the 24-hour time point recurrence question indicates headache recurrence between 2 and 24 hours but the 48-hour time point recurrence question indicates either no or a less severe headache recurrence between 2 and 48 hours.

[redacted]









For sustained efficacy endpoints (sustained pain freedom and sustained pain relief from 2 to 24 and 48 hours after the initial dose), the primary analysis will only include participants for whom the sustained efficacy endpoint in question can be determined based on all available data on headache severity, headache recurrence, use of rescue medication, and use of optional second dose. Figure 5-5 to Figure 5-8 show the diagrams for determining the sustained efficacy endpoints based on all available data.

Figure 5-5 Determination of sustained pain freedom from 2 to 24 hours after the initial dose

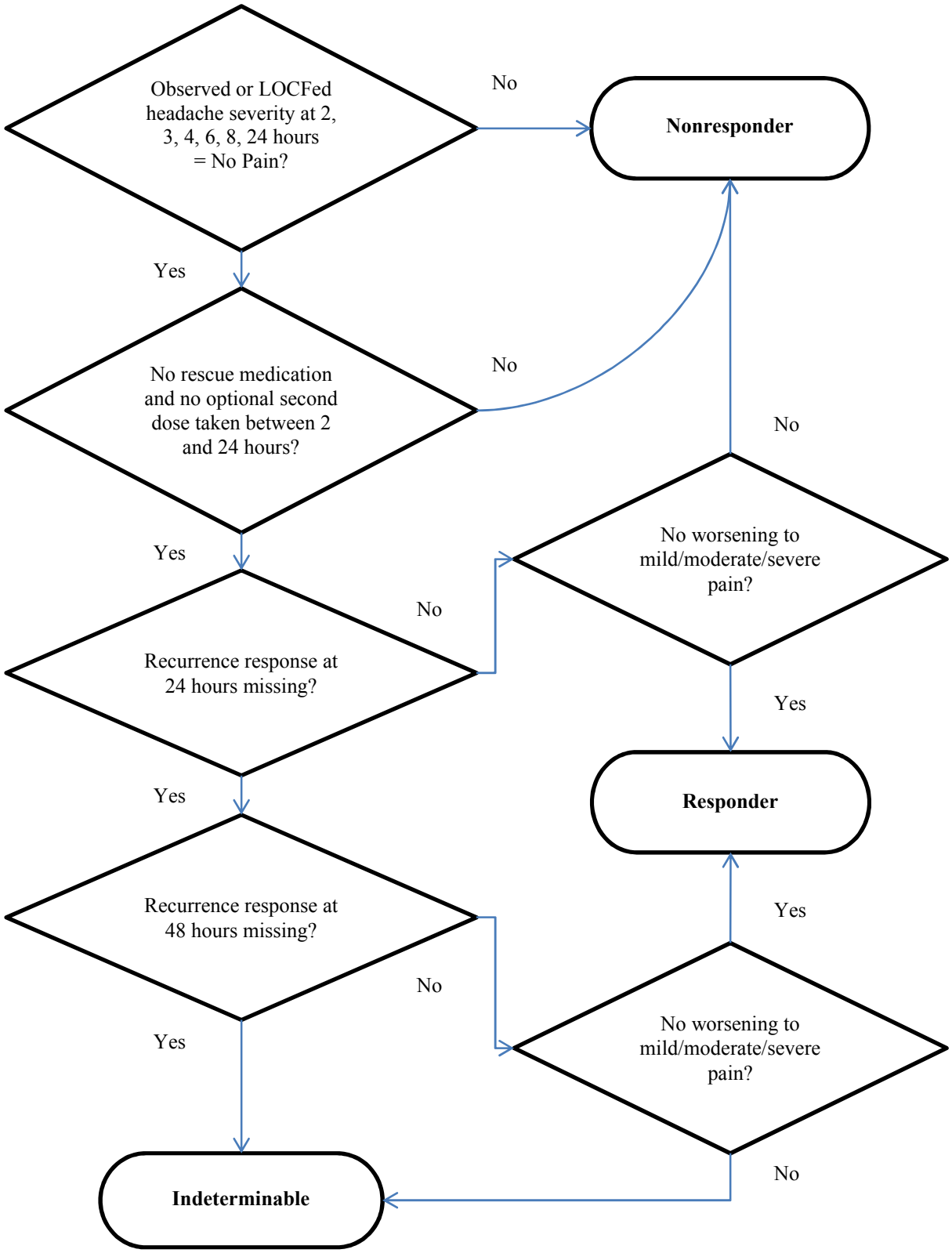


Figure 5-6 Determination of sustained pain relief from 2 to 24 hours after the initial dose

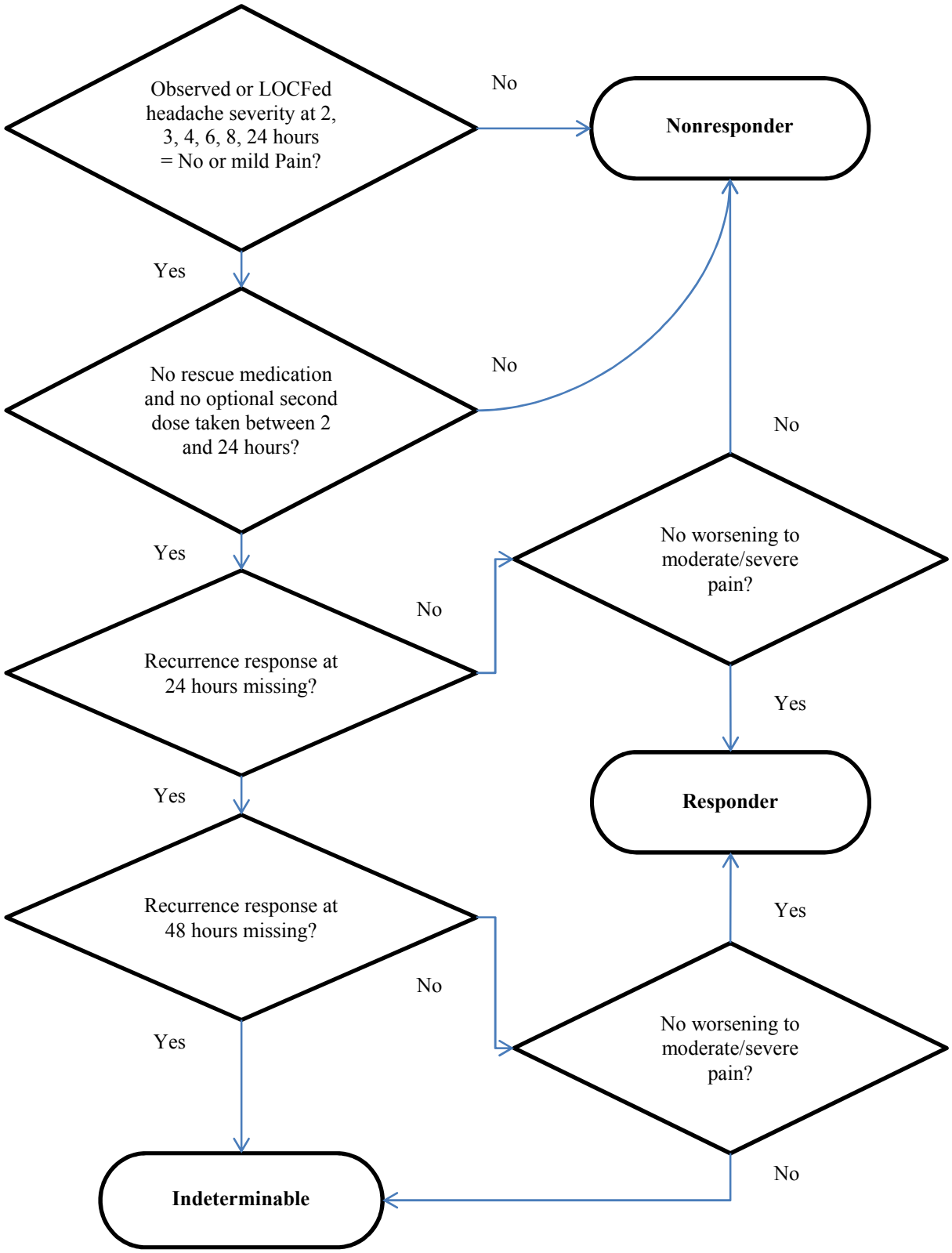


Figure 5-7 **Determination of sustained pain freedom from 2 to 48 hours after the initial dose**

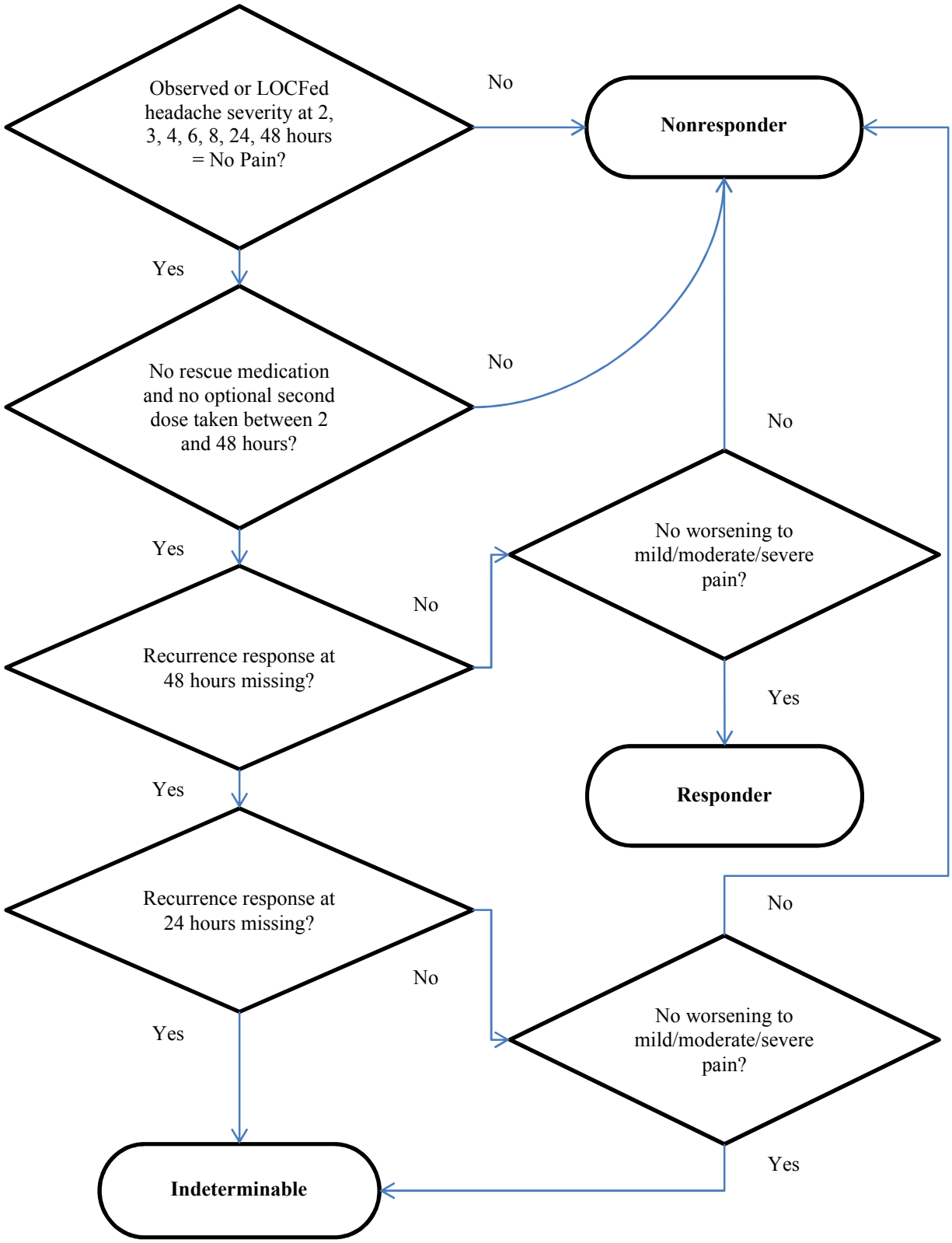
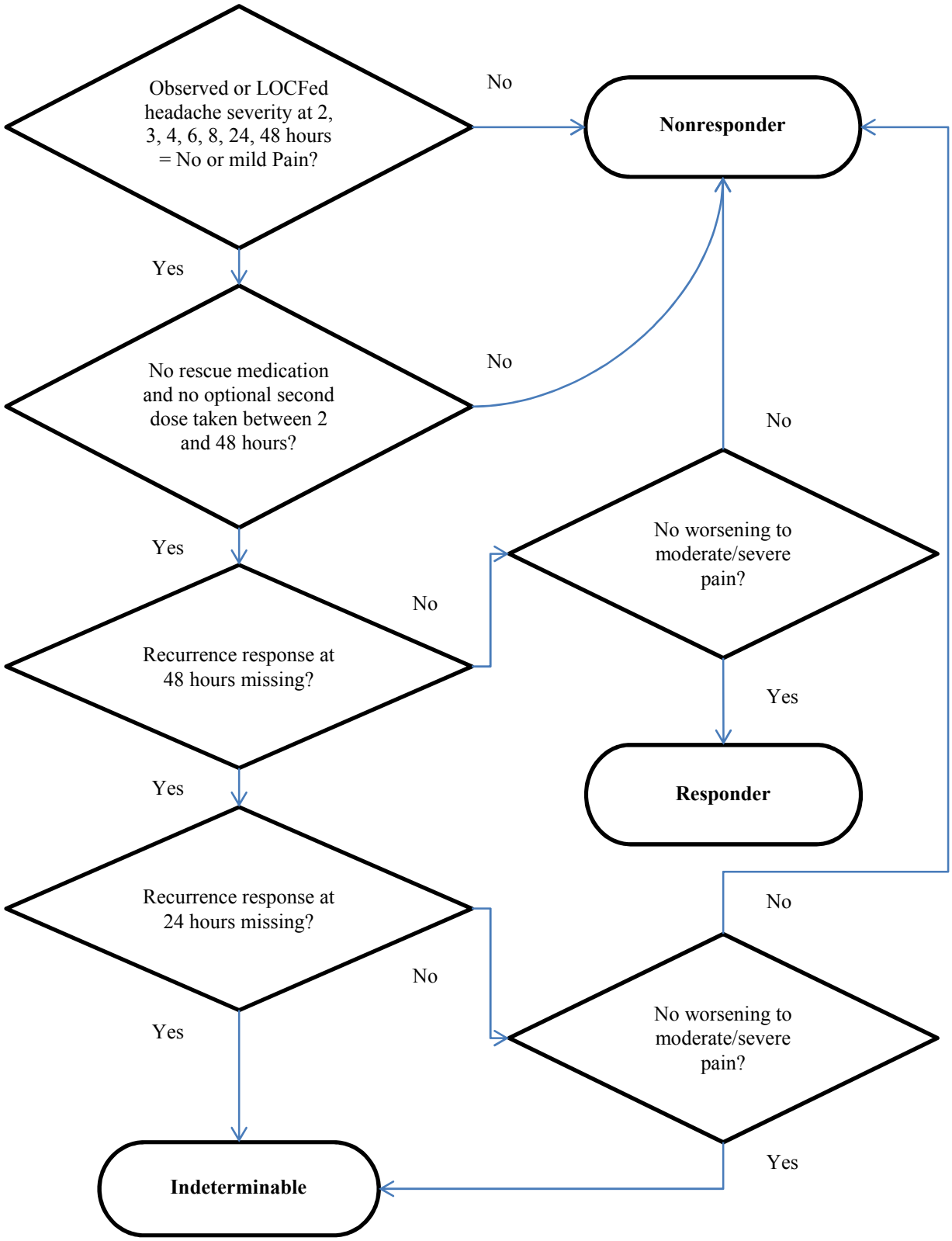


Figure 5-8 Determination of sustained pain relief from 2 to 48 hours after the initial dose



[redacted]

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

The distribution of participants within the analysis populations will be summarized as follows:

Table 5-4 Analysis Population Summaries

Population	Description	Timing	Methodology
Screened Population	Distribution overall and within sites in total	—	Categorical counts
ITT, mITT, and Safety populations	Distribution overall and within sites in total and by treatment group	—	Categorical counts

5.1.1.2.2 Participant Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Participant disposition will be summarized as follows:

Table 5-5 Participant Disposition Summaries

Parameter	Description	Timing	Methodology
Screening disposition[1]	Distribution in the Screened Population in total	Screening Period	Categorical descriptives
Double blind disposition[1]	Distribution in the Safety Population and ITT Population in total and by treatment group	Double Blind Period	Categorical descriptives
4 Week Safety Follow-up disposition[1]	Distribution in the Safety Population and ITT Population in total and by treatment group	Post-treatment Period	Categorical descriptives

[1] Participant disposition will be listed and participants who prematurely discontinued will be listed.

5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. Protocol deviations will be summarized as follows:

Table 5-6 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Major protocol deviations[1]	Distribution in the ITT Population in total and by treatment group	—	Categorical descriptives

[1] Protocol deviations will be listed.

5.1.1.2.4 Demographics

Demographics will be summarized in total and by treatment group for the ITT, Safety, and mITT populations, as follows:

Table 5-7 Demographic Summaries

Parameter	Description	Timing	Methodology
Age[1]	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• <20 • 20 to 29 • 30 to 39 • 40 to 49 • 50 to 59 • 60 to 69 • >= 70	Informed consent	Categorical descriptives

Sex, race, and ethnicity[1]	• eCRF categories
	• Race group
	  ○ White
	  ○ Non-white
		Screening Period	Categorical descriptives

[1] Participant demographics will be listed.

5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by treatment group for the ITT, Safety, and mITT populations as follows:

Table 5-8 Baseline Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics[1]	• Height (m) • Weight (kg) • Body mass index (BMI) ○ Weight (kg) / height (m)^2	Latest assessment in Screening Period	Continuous descriptives
Randomization strata[2]	• Previous response to triptans (Triptan Responder, Triptan Insufficient Responder, Triptan Naïve)	Randomization date	Categorical descriptives

Parameter	Description	Timing	Methodology
	• Current use of prophylactic concomitant medication for migraine (Yes, No)		
Baseline efficacy	Endpoints and timing fully described in Section 5.1.1.3 • migraine headache severity • migraine-associated symptom • most bothersome migraine-associated symptom by symptom Summary for mITT Population only	Predose	Categorical descriptives
Cardiovascular risk	• Cardiovascular risk factor subgroup (low risk, moderate risk, high risk) Summary for Safety Population only	Randomization date	Categorical descriptives

[1] Participant baseline characteristics will be listed.
[2] Participant randomization scheme and codes will be listed.

5.1.1.2.6 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer. Unique participants who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by treatment group for the Safety Population as follows:

Table 5-9 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history[1]	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.
[1] Participant medical history will be listed.

5.1.1.2.7 Migraine History

Migraine history, including diagnosis, duration of disorder, previous use of prophylaxis treatment, average frequency of moderate to severe migraines per month in past 3 months, and acute treatments will be reported in total and by treatment group for the Safety Population as follows:

Table 5-10 Medical History Summary

Parameter	Description	Timing	Methodology
Migraine Diagnosis[1]	With Aura, Without Aura, Both	Screening Period	Categorical descriptives
Previous Prophylaxis Migraine Treatment[1]	Yes or No	Screening Period	Categorical descriptives
Acute Migraine Treatment[1]	Categorize as Yes or No, and subcategorize the Yes by:	Screening Period	Categorical descriptives

Parameter	Description	Timing	Methodology
	• Triptan • Ergot or Ergot Combinations • NSAID • Opiate or Opiate Combination • Antiemetic Agent • Barbiturates • Other		
Migraine Disorder Duration[1]	In the Table summarize in Years, in the Listing show original data in Years and Months	Screening Period	Continuous descriptives
Average Frequency of Moderate to Severe Migraines per Month in Last 3 Months	**N/A**	Screening Period	Continuous descriptives

[1] Participant migraine history will be listed.

5.1.1.2.8 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version March 2016 or newer. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by treatment group for the Safety Population as follows:

Table 5-11 Medication Summaries

Parameter	Description	Timing	Methodology
Prior medications[1]	Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant medications[1]	Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment Period	Categorical descriptives

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.
[1] Participant prior and concomitant medication will be listed.

5.1.1.3 Efficacy and Pharmacokinetic Analyses

Efficacy analyses will be based on the mITT Population.

The following efficacy assessments and terms are defined:

Table 5-12 Efficacy Assessments

Assessment/Term	Description
Rating of Headache Severity[1]	Headache severity will be subjectively rated by the participant at predefined timepoints (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose) on a scale from no pain to severe pain: • No pain • Mild pain • Moderate pain • Severe pain
Use of Rescue Medication[1]	Any rescue medication taken within 48 hours after treating their migraine attack with IP, in addition documenting the date and time that the rescue medication was taken. • Recorded by participants in e-diary
Use of Optional Second Dose and Recurrence of Headache Pain[1]	Optional second dose of IP due to inadequate response to their initial dose of IP. Date and time of the second dose will be reported, as well as pain severity and absence or presence of migraine-associated symptoms at the time the second dose is taken and 2 hours after taking the second dose. The incidence of recurrence in participants who had pain relief and pain freedom at 2 hours after the initial dose will be collected. • Recorded by participants in e-diary
Migraine-associated symptoms[1]	Absence or presence of migraine-associated symptoms: photophobia, phonophobia, nausea, and vomiting • Completed by the participant in e-diary
[redacted]	[redacted]

[1] Participant efficacy parameters will be listed.

Baseline assessments for applicable efficacy endpoints are defined as follows:

Table 5-13 Efficacy Endpoint Baseline Definitions

Endpoint	Description	Timing
Baseline rating of headache severity	Headache severity rating (Moderate, Severe)	pre-dose
Baseline migraine-associated symptom	Migraine-associated symptom • Photophobia (Yes, No) • Phonophobia (Yes, No) • Nausea (Yes, No) • Vomiting (Yes, No)	pre-dose

5.1.1.3.1 Endpoints for US

The efficacy endpoints for the United States analyses are described as follows. [redacted]

Table 5-14 US Analyses

Endpoint	Description	Timing	Methodology
P1	Pain freedom (PF) at 2 hours after the initial dose, defined as a reduction in headache severity from moderate/severe at baseline to no pain, at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
P2	Absence of the most bothersome migraine-associated symptom (the most bothersome migraine-associated symptom will be identified at baseline for each participant) at 2 hours after the initial dose.	2 hours after the initial dose	Logistic regression model
S1	Pain relief (PR) at 2 hours after the initial dose, defined as the reduction of a moderate/severe migraine headache to a mild headache or to no headache, at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
S2	Sustained pain relief (SPR) from 2 to 24 hours after the initial dose, defined as pain relief with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a moderate/severe headache during the relevant number of hours after dosing with the IP	2 to 24 hours after the initial dose	Logistic regression model
S3	Sustained pain freedom (SPF) from 2 to 24 hours after the initial dose, defined as pain freedom with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a mild/moderate/severe headache during the relevant number of hours after dosing with the IP	2 to 24 hours after the initial dose	Logistic regression model
S4a	Absence of photophobia at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
S4b	Absence of phonophobia at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
S4c	Absence of nausea at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 5-15 EU Analyses

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Endpoint	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A summary of the number and percentage of participants who took both the optional second dose and rescue medication within 24 (48) hours after the initial dose will also be provided by treatment sequence (placebo/placebo, ubrogepant 25 mg/25 mg, ubrogepant 25 mg/placebo, ubrogepant 50 mg/50 mg, ubrogepant 50 mg/placebo). The denominator is the number of participants who took the optional second dose.

[redacted]

5.1.1.3.4 Multiple Comparisons Procedure for Primary and Secondary Endpoints

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for the set of primary and secondary endpoint comparisons between each dose level of ubrogepant vs. placebo both for the US analyses and for the EU analyses.

A graphical approach by Bretz et al (2009) will be used to control the overall type I error rate for multiple comparisons across the ubrogepant doses and the primary and secondary efficacy endpoints. For the US analyses, the coprimary efficacy endpoints will serve as the gatekeepers of the secondary endpoints. [redacted]. The secondary endpoints will be tested in the same order as they appear in the list of secondary endpoints, except for the 2 migraine-associated symptoms, photophobia and phonophobia, which will be treated at the same level to allow the recycling of weights among the 2 symptom endpoints. Recycling of weights between the 2 doses from nausea to pain freedom is also allowed.

Using graphical approach with the weighted Bonferroni-based closed test procedure, the endpoints are represented by circles with associated weights inside the circle. The weight is the fraction of α, representing local significance levels. The fraction in the rectangle, associated with a line connecting two circles, indicates the fraction of the local significance level of the circle at the beginning of the line which is added to the local significance level of the circle at the end of the line, if the null hypothesis at the beginning circle is rejected.

Figure 5-9 Multiple Comparisons Procedure for the US

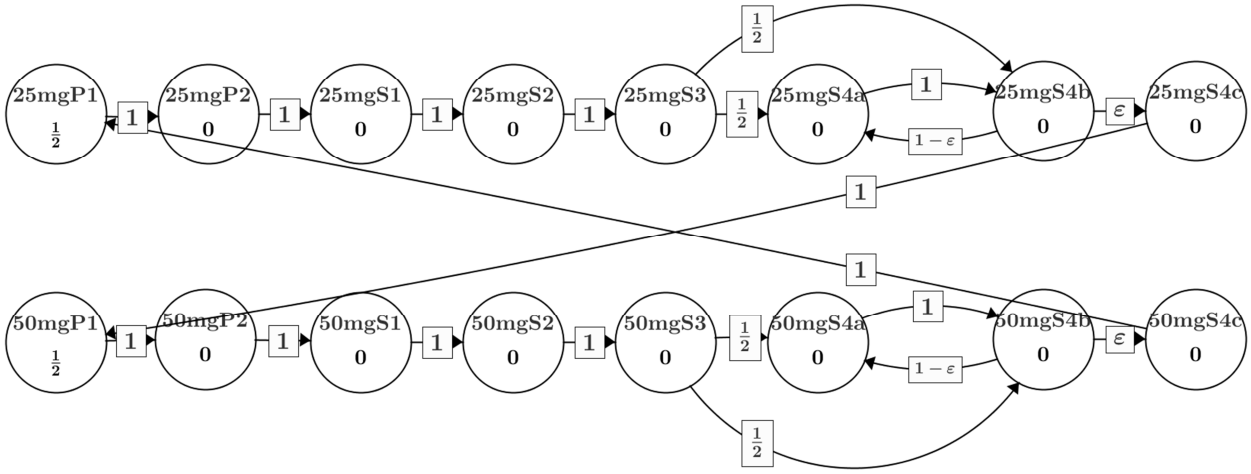
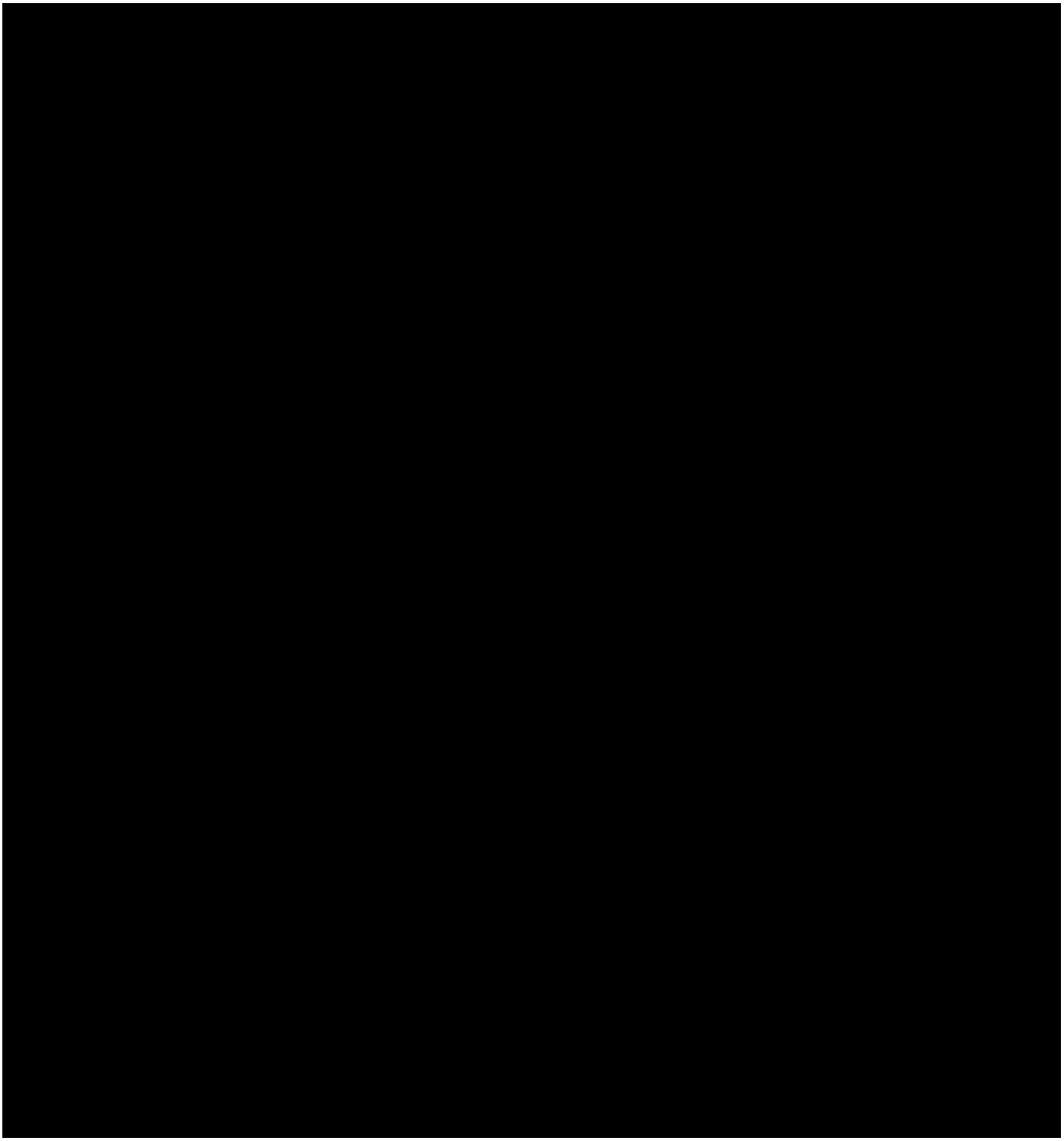


Table 5-16 Multiple Comparisons Procedure Definitions for the US

Circle	Alternative Hypothesis	Objective	Weight	Local Significance Level
25mgP1	Primary Efficacy Endpoint 1 for 25 mg ubrogepant is significantly different from placebo	PO1	1/2	α*(1/2) = α/2
25mgP2	Primary Efficacy Endpoint 2 for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS3	Secondary Efficacy Endpoint 1 for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS1	Secondary Efficacy Endpoint 2 for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS2	Secondary Efficacy Endpoint 3 for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS4a	Secondary Efficacy Endpoint 4a for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS4b	Secondary Efficacy Endpoint 4b for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
25mgS4c	Secondary Efficacy Endpoint 4c for 25 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mgP1	Primary Efficacy Endpoint 1 for 50 mg ubrogepant is significantly different from placebo	PO1	1/2	α*(1/2) = α/2
50mgP2	Primary Efficacy Endpoint 2 for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mgS3	Secondary Efficacy Endpoint 1 for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0

50mgS1	Secondary Efficacy Endpoint 2 for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mgS2	Secondary Efficacy Endpoint 3 for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mgS4a	Secondary Efficacy Endpoint 4a for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mgS4b	Secondary Efficacy Endpoint 4b for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0
50mS4c	Secondary Efficacy Endpoint 4c for 50 mg ubrogepant is significantly different from placebo	PO1	0	α*0 = 0



[redacted]

5.1.1.4.1 Study Treatment Exposure and Compliance

Study treatment exposure will be summarized and listed for the Safety Population.

The summary of treatment exposure will include the number and percentage of participants who took the initial dose only, the number and percentage of participants who took both the initial dose and the optional second dose, and the number and percentage of participants who took the PK dose for each treatment group.

The listing of treatment exposure will indicate whether the participant took the optional second dose and [redacted] in addition to the first dose.

Treatment compliance to the first dose of study medication will not be calculated as participants are only to take 1 tablet.

[redacted]

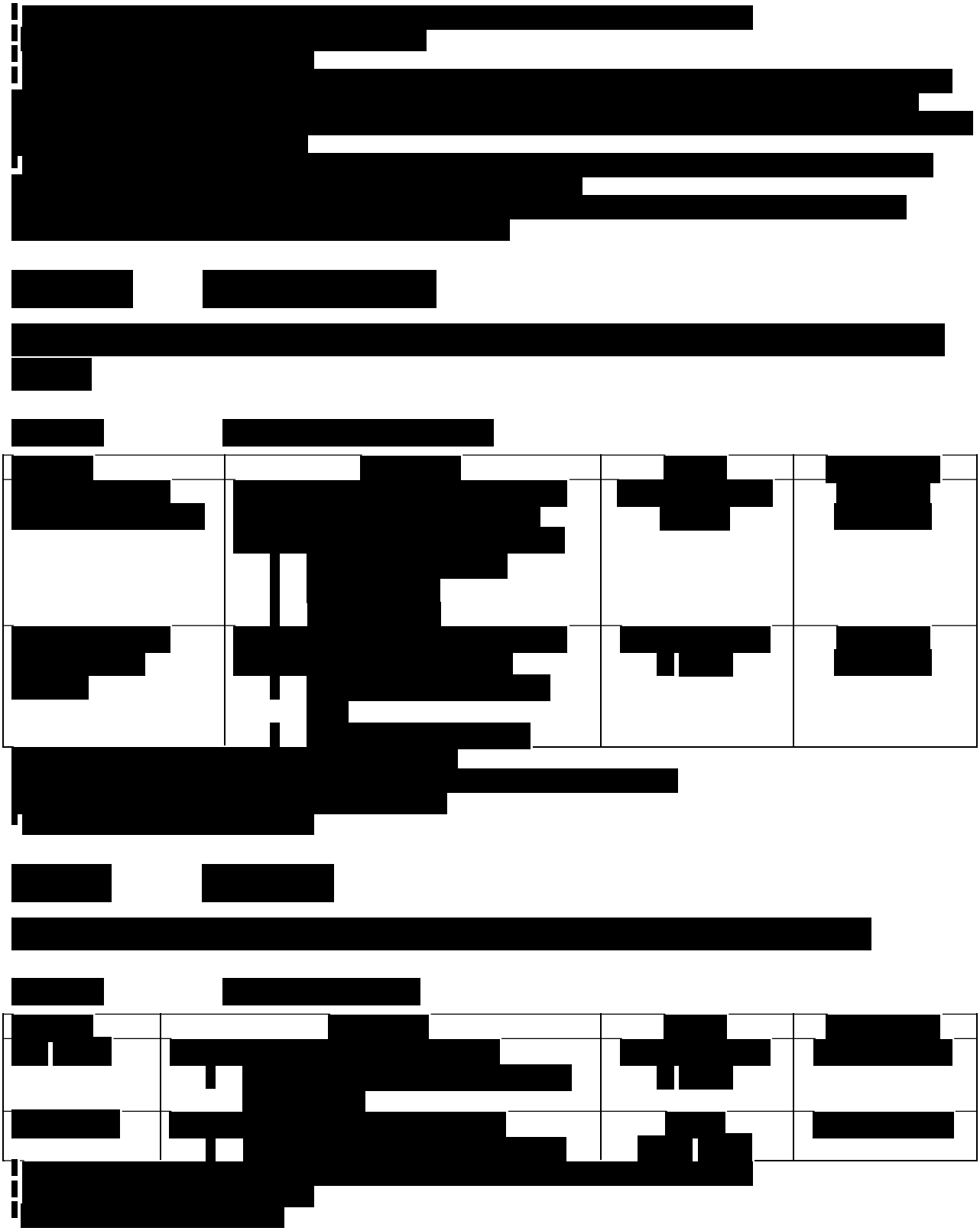
[redacted]

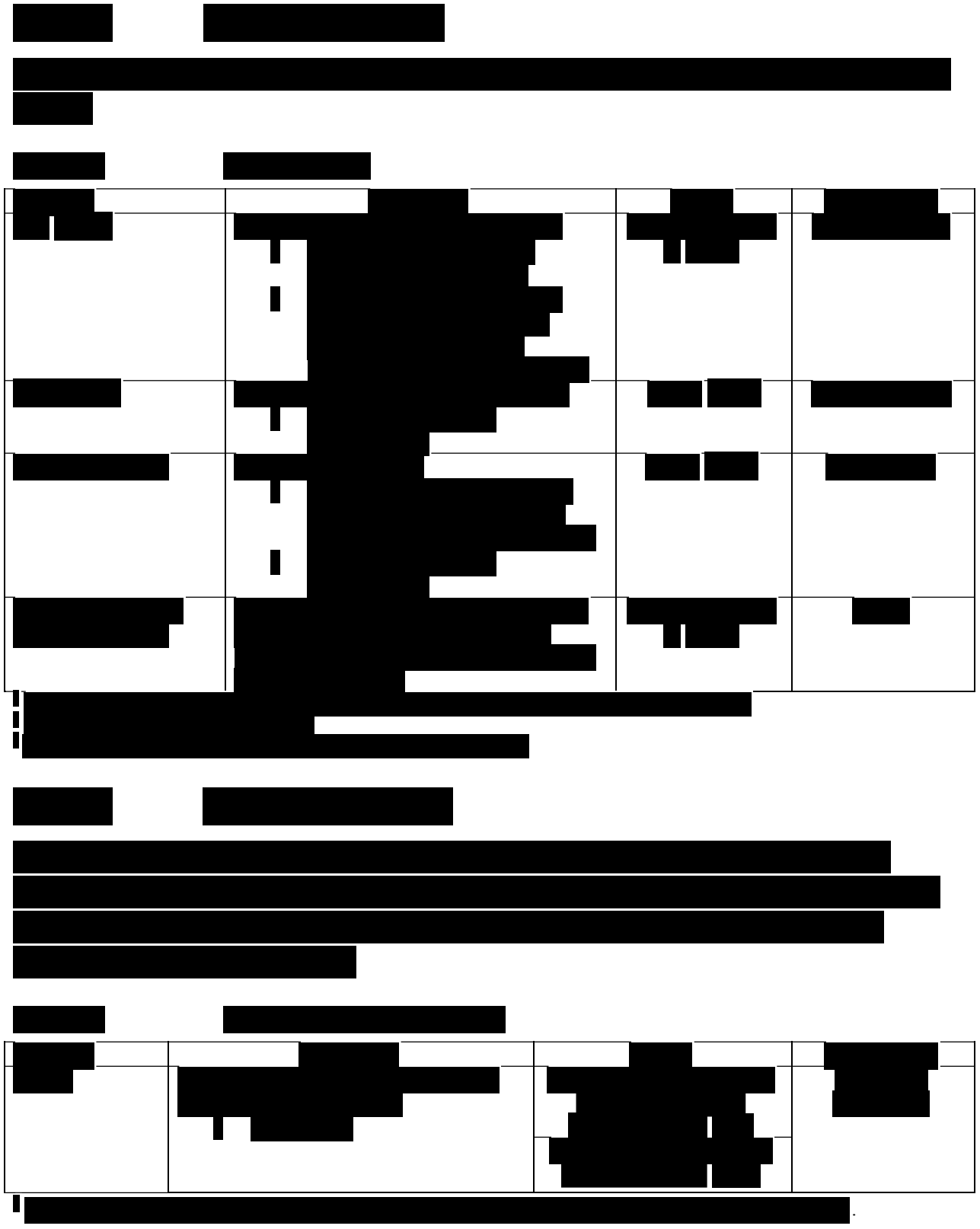
Parameter	Description	Timing	Methodology
[redacted]	[redacted]	[redacted]	[redacted]

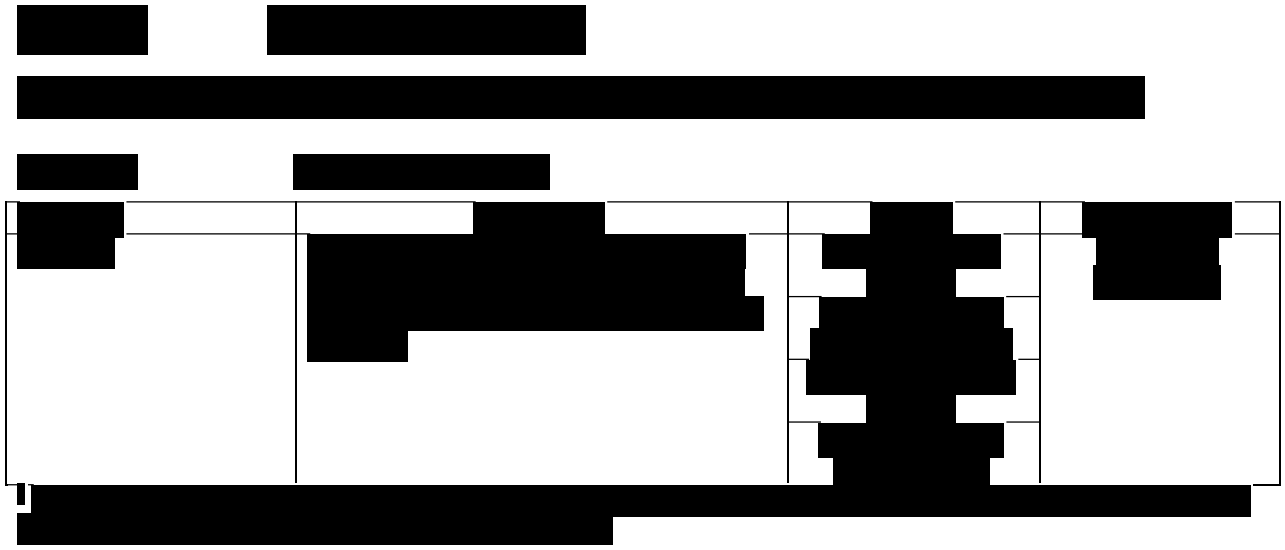
[redacted]

[redacted]

[redacted]







5.1.1.5 Subgroup Analyses

The following subgroup analyses will be conducted by historical triptan response. PF and absence of the most bothersome migraine-associated symptom at 2 hours after initial dose will be analyzed using similar models as the primary endpoints with the additional treatment group by historical triptan response interaction. Time to PF and absence of the most bothersome migraine-associated symptom within 2 hours after the initial dose will be analyzed by historical triptan response separately.

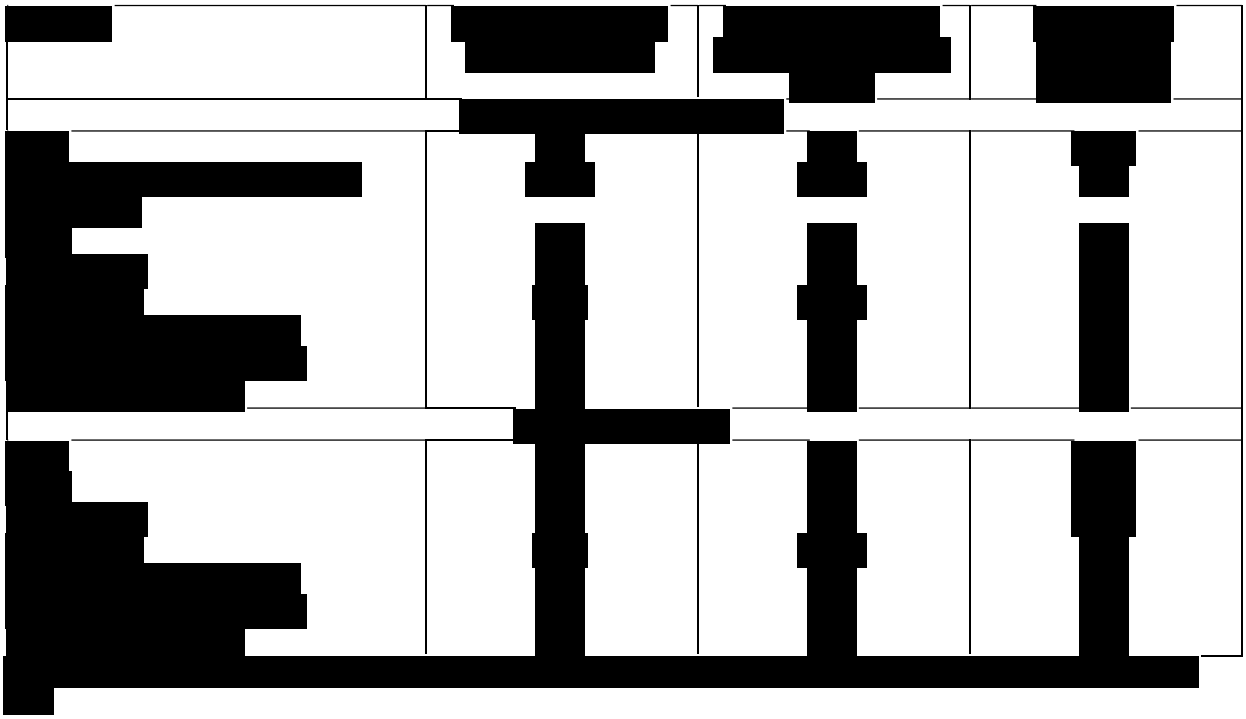
- ***PF at 2 hours after initial dose***
- ***Absence of the most bothersome migraine-associated symptom at 2 hours after initial dose (US only)***
- ***Time to PF within 48 hours after the initial dose***
- ***Time to absence of the most bothersome migraine-associated symptom within 48 hours after the initial dose (US only)***

A pooled analysis among triptan insufficient responders across ubrogepant pivotal studies will be conducted to demonstrate statistically significant efficacy in the triptan insufficient responders' population.

5.1.1.6 Interim Analyses

Not applicable.

[redacted]



5.2 Changes in the Conduct of the Study or Planned Analyses

Prior to database lock, there were no changes in study conduct or planned analyses from what was described in the protocol and detailed in the SAP.

5.2.1 Changes in the Conduct of the Study

Not applicable.

5.2.2 Changes to Analyses Prior to Database Lock

Not applicable.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment day is defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description
Treatment Day	Relative to treatment start date If analysis date ≥ treatment start date: • Day = analysis date – treatment start date + 1 o Day 1 = treatment start date If analysis date < treatment start date: • Day = analysis date – treatment start date o Day -1 = day before treatment start date o There is no Day 0

6.1.2 Missing/Incomplete Treatment End Date

If the investigator is unable to provide the treatment end date, treatment end date will be imputed to the last available dosing record date.

6.2 Analysis Visit Windows

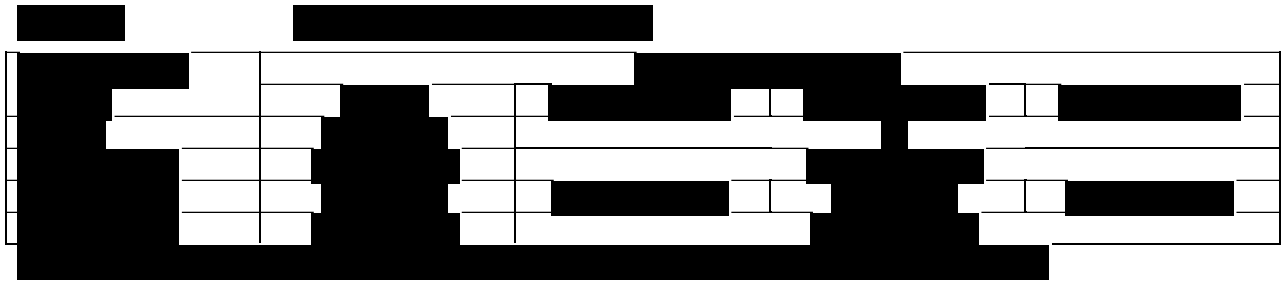
6.2.1 Efficacy

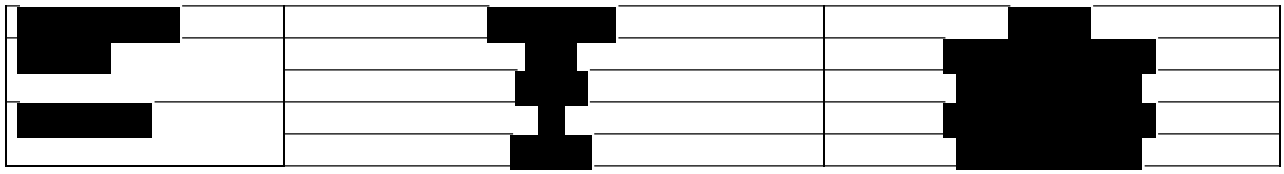
The analysis visit windows for efficacy endpoints are defined as follows:

Table 6-2 Efficacy Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Study Hour (eDiary)	Window
Pretreatment	Baseline	Pre-dose	Based on nominal timepoints recorded in eDiary
Treatment	0.5 hour post-dose	0.5 hour post-dose	
	1 hour post-dose	1 hour post-dose	
	1.5 hours post-dose	1.5 hours post-dose	
	2 hours post-dose	2 hours post-dose	
	3 hours post-dose	3 hours post-dose	
	4 hours post-dose	4 hours post-dose	
	6 hours post-dose	6 hours post-dose	
	8 hours post-dose	8 hours post-dose	
	24 hours post-dose	24 hours post-dose	
	48 hours post-dose	48 hours post-dose	

[redacted]





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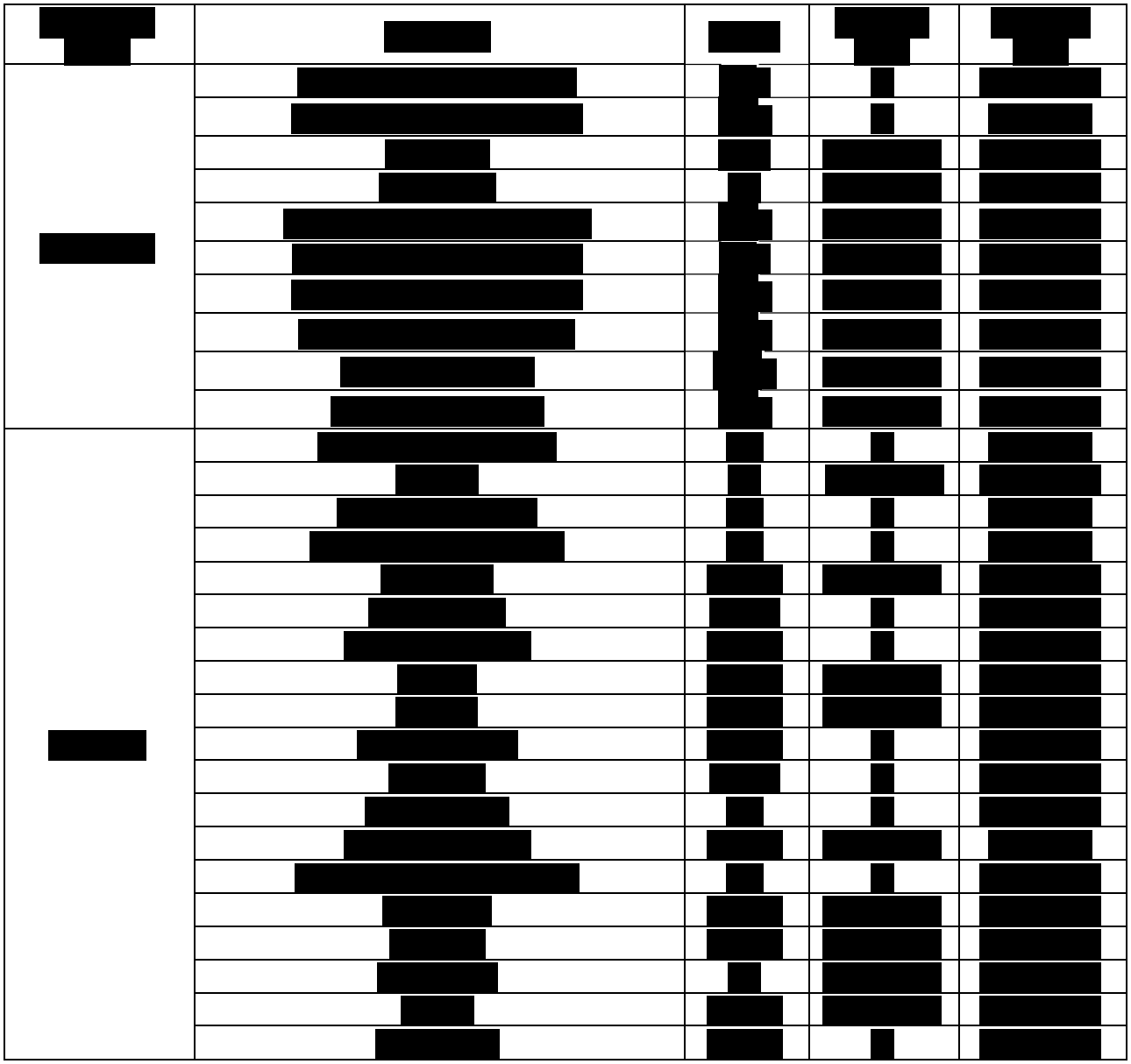

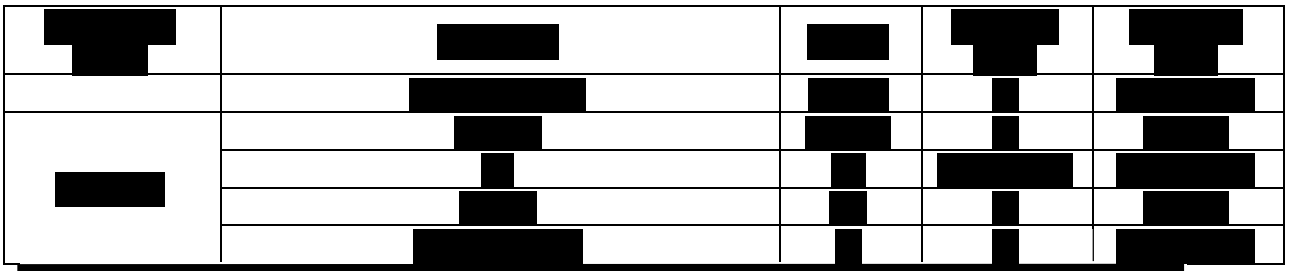

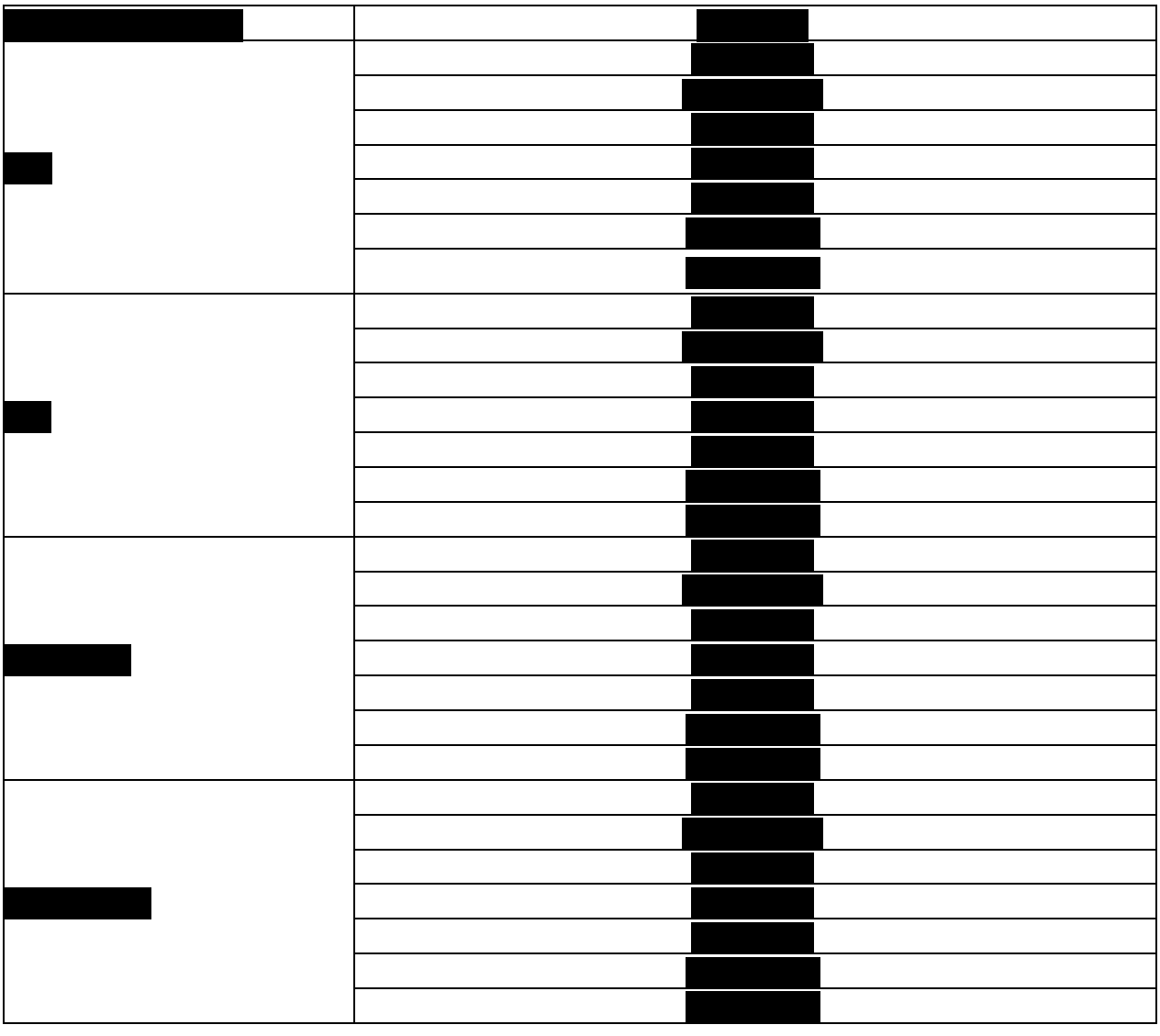

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6.4 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

7. References

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28:586–604.

Firth D. Bias reduction of maximum likelihood estimates. Biometrika.1993;80:27–38.

Grundy SM, Cleeman JI, Bairey Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB, Pasternak RC, Smith Jr SC, and Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll of Cardiology. 2004;44:720-732.

Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002;21:2409-2419.

National Cholesterol Education Program Adult Treatment Panel III Guidelines. NIH Publication No. 01-3670, May 2001. http://www.scymed.com/en/smnxdj/edzr/edzr9610.htm

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UBR-MD-02

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

STATISTICAL ANALYSIS PLAN AMENDMENT

SUMMARY OF CHANGES

Original SAP Date: **17 May 2017**

Amendment #1: **21 March 2018**

1 AMENDMENT #1 TO STATISTICAL ANALYSIS PLAN for UBR-MD-02

1.1 Introduction

Amendment #1 specifies the following changes to the original Statistical Analysis Plan (SAP) for Study UBR-MD-02, dated 17 May 2017:

- Adding 9 other efficacy endpoints in Table 4-1 Study Objectives and Corresponding Endpoints
- Adding proportional odds model analysis in Table 5-2 Statistical Methodology
- Updating missing data handling for headache recurrence endpoints
- Adding 9 endpoints in Table 5-14 US Analyses and 4 endpoints in [redacted]
- Updating Figure 5-9 Multiple Comparisons Procedure for the US [redacted]
- Updating Section 5.1.1.4.1 Study Treatment Exposure and Compliance
- [redacted]
- Adding subgroup analyses in Section 5.1.1.5 Subgroup Analyses
- [redacted]

- Minor editorial changes

1.2 Global Changes

None.

1.3 Sections Deleted

None.

1.4 Sections Added

None.

1.5 Revisions

1.5.1 Table 4-1, Study Objectives and Corresponding Endpoints (Pages 11-14)

Rationale: This section has been amended to reflect adding 9 other efficacy endpoints to the list of other efficacy endpoints.

[redacted]

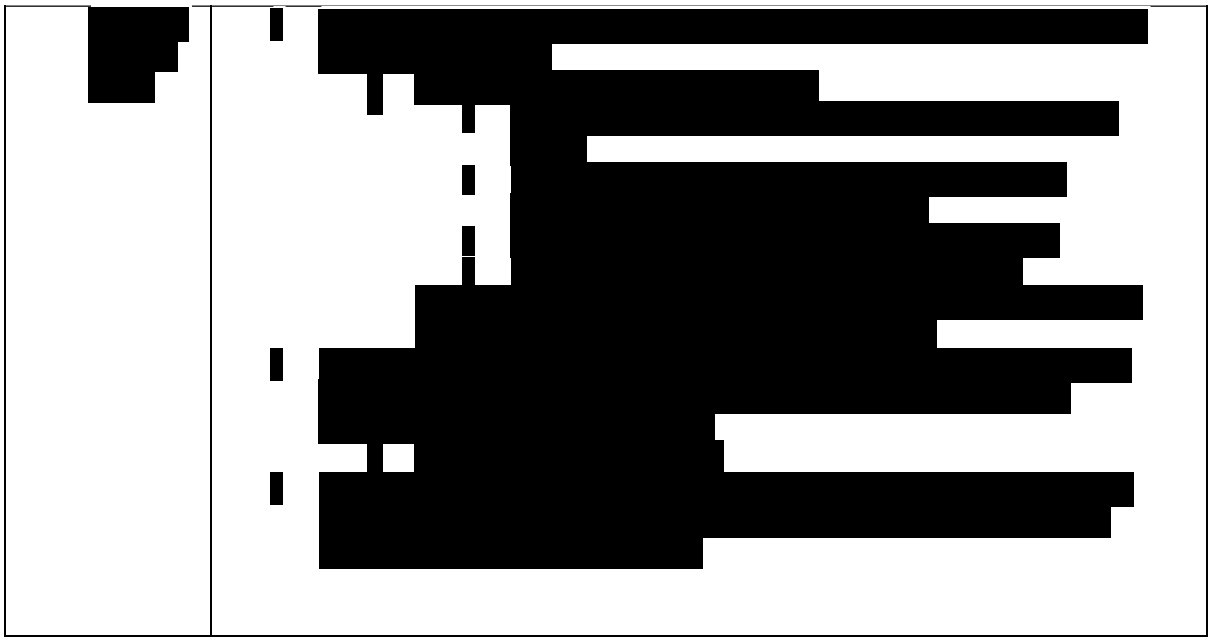
[redacted]

[redacted]

1.5.2 Table 5-2, Statistical Methodology (Page 20-21)

Rationale: This table has been amended to add the proportional odds model for the analysis of pain severity at 2 hours after the initial dose.

[redacted]



1.5.3 Section 5.1.1.1.4, Missing Data (Pages 21-31)

Rationale: This section has been amended to update the missing data handling of sustained efficacy endpoints.

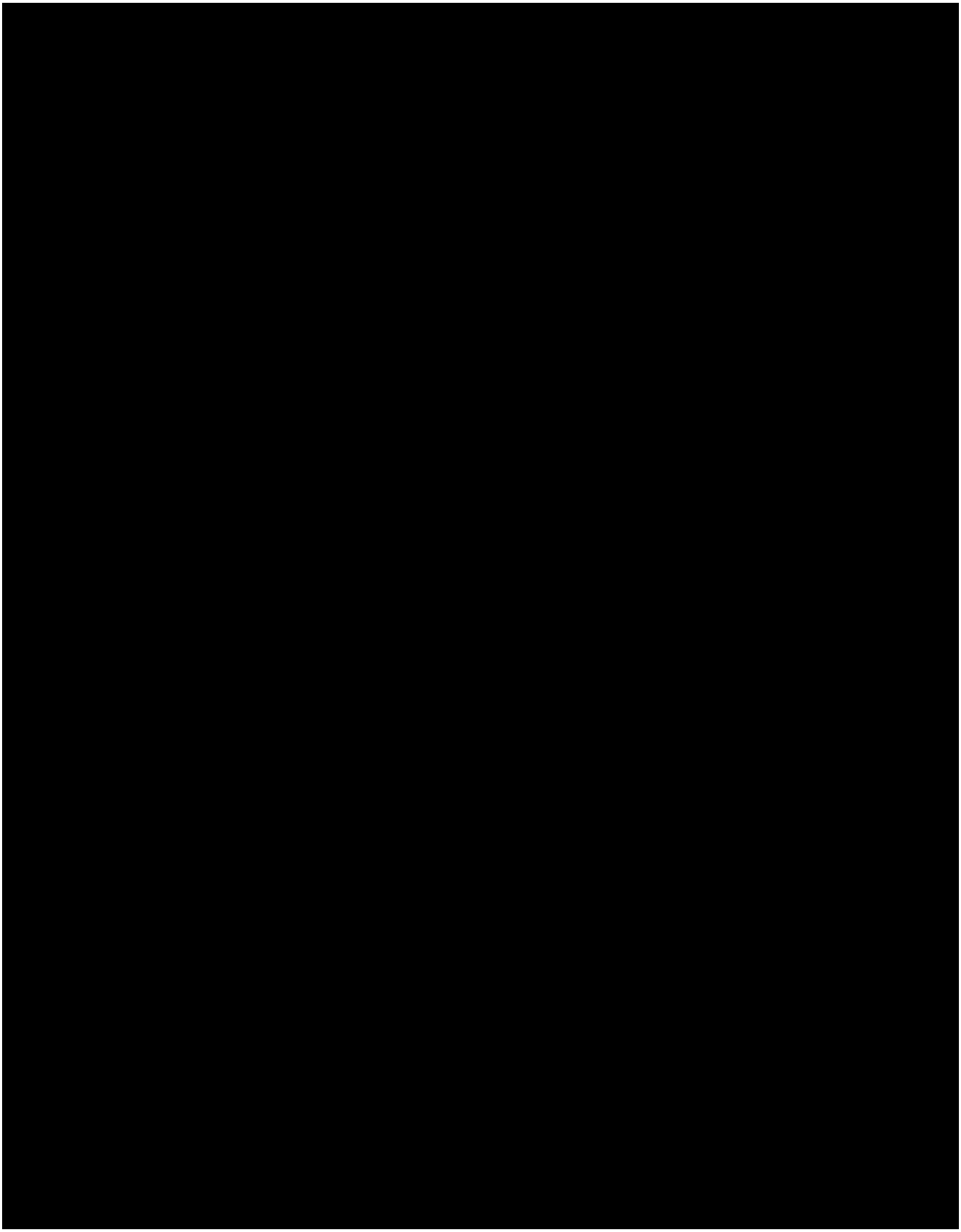
The missing data section now reads as follows:

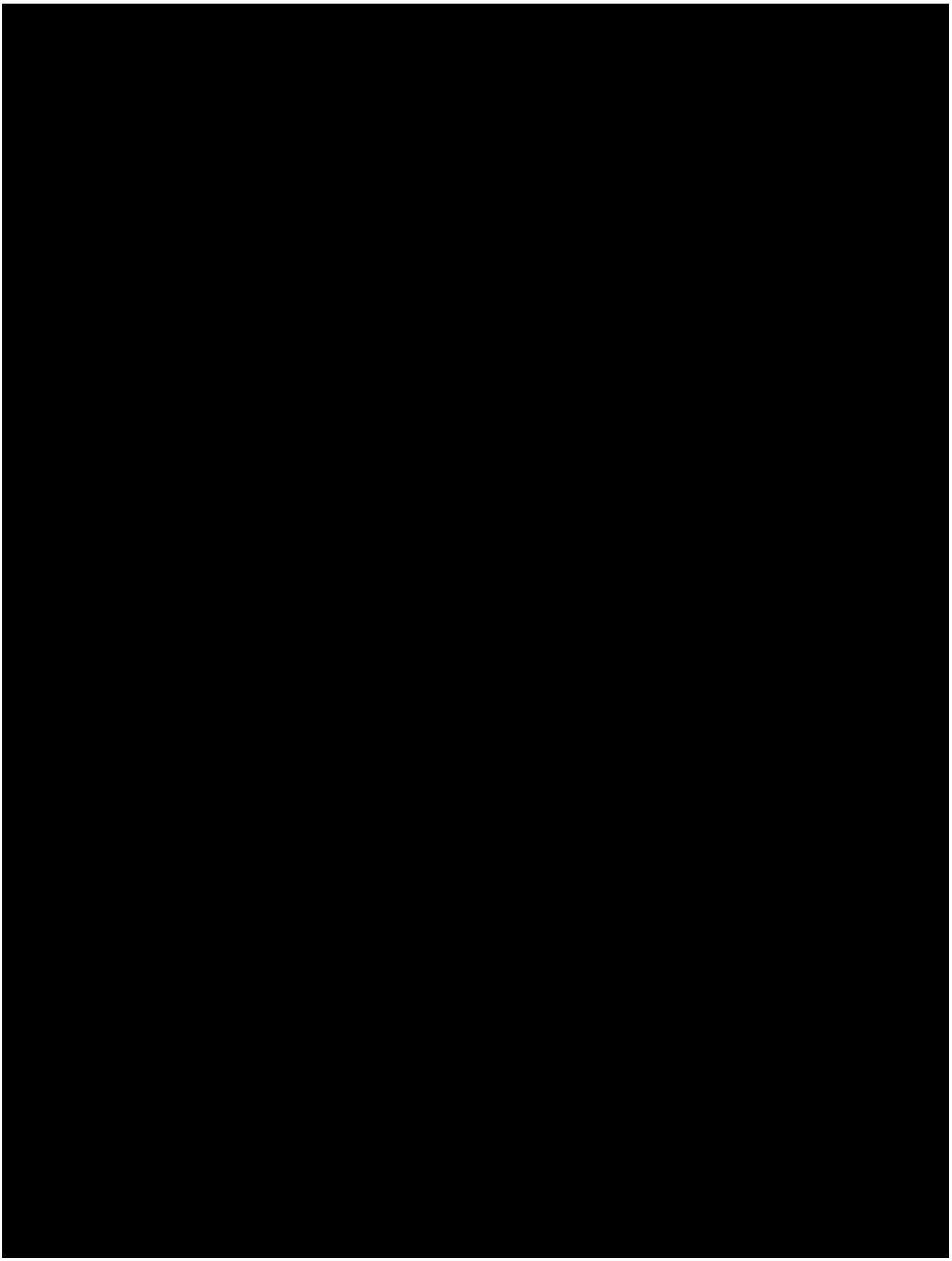
General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

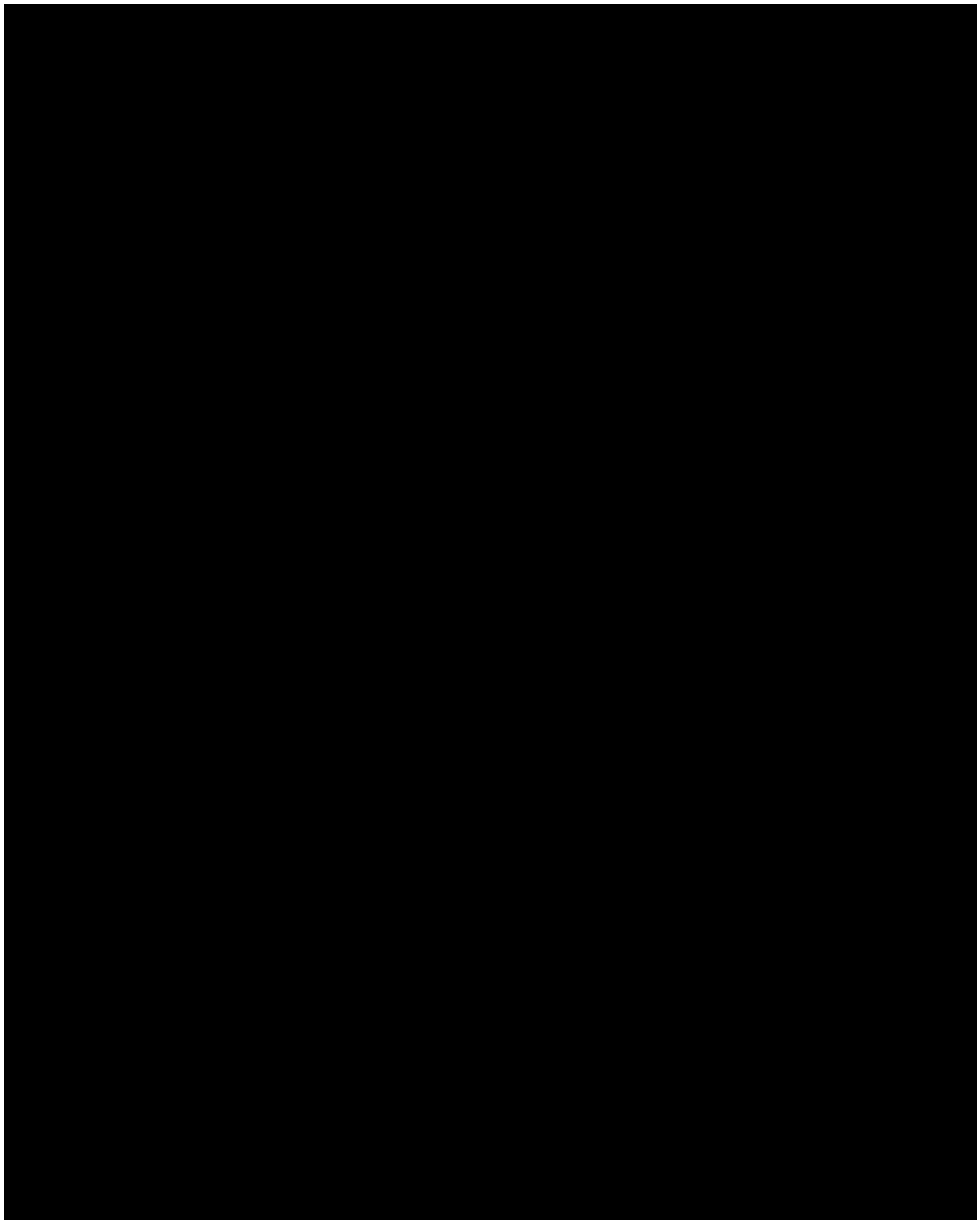
Table 5-3 Missing Data Handling by Endpoint Type

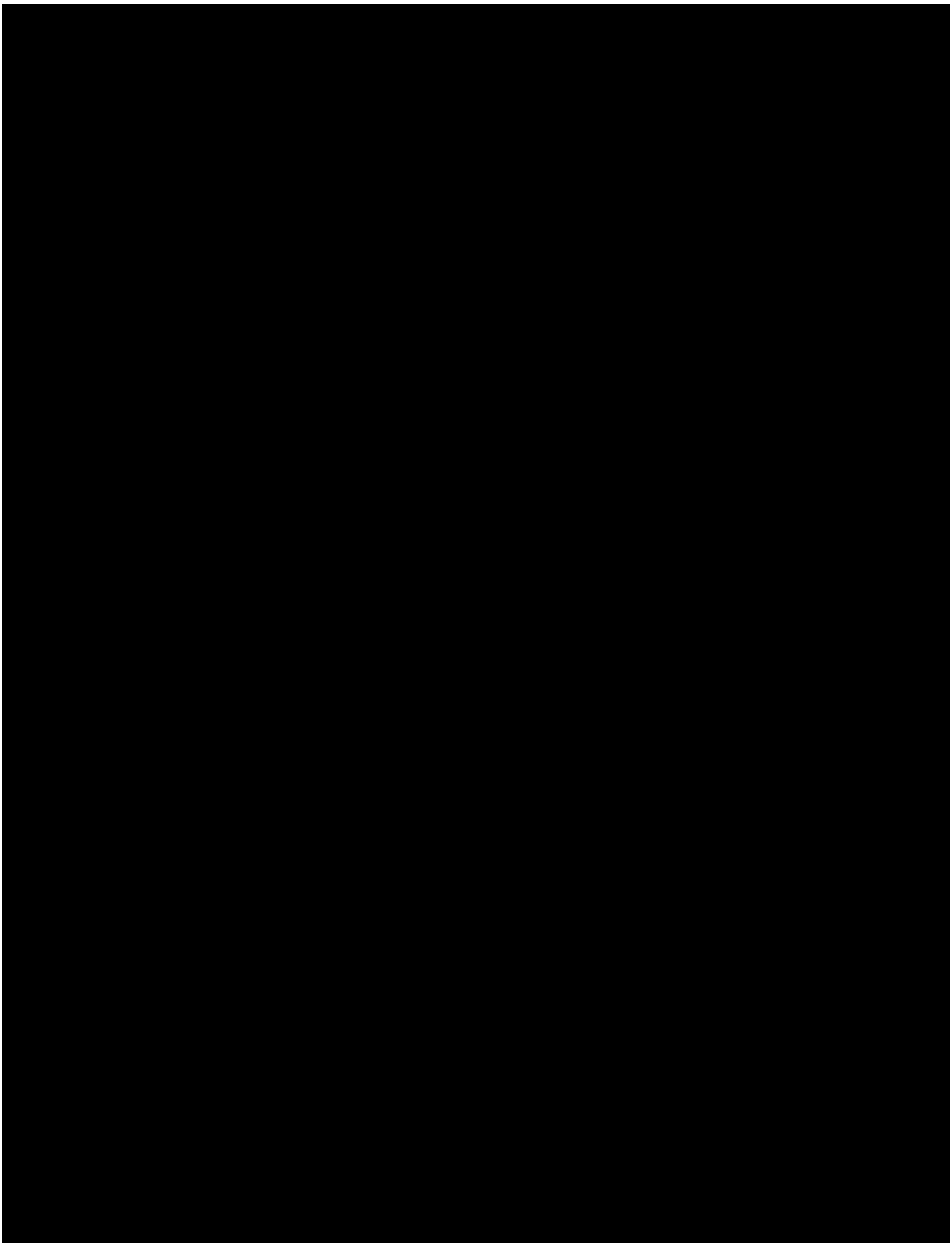
Parameter type	Timing	Missing Data Handling
[redacted]	[redacted]	[redacted]
Responder	Treatment Period	• If missing headache severity, migraine-associated symptoms, satisfaction with study medication, or functional disability scale at scheduled postdose time points, use LOCF • Sensitivity analysis for the primary efficacy endpoints is to impute participants with missing data at 2 hours as non-responders, provided that the participant has at least 1 postdose value before 2 hours after the initial dose
[redacted]	[redacted]	[redacted]

A conservative approach will used to resolve the incompatibility between the answers to the headache recurrence questions at the 24- and 48-hour time points by setting the answer to the recurrence question at the 48-hour time point the same as the answer to the recurrence question at the 24-hour time point, when the 24-hour time point recurrence question indicates headache recurrence between 2 and 24 hours but the 48-hour time point recurrence question indicates either no or a less severe headache recurrence between 2 and 48 hours.









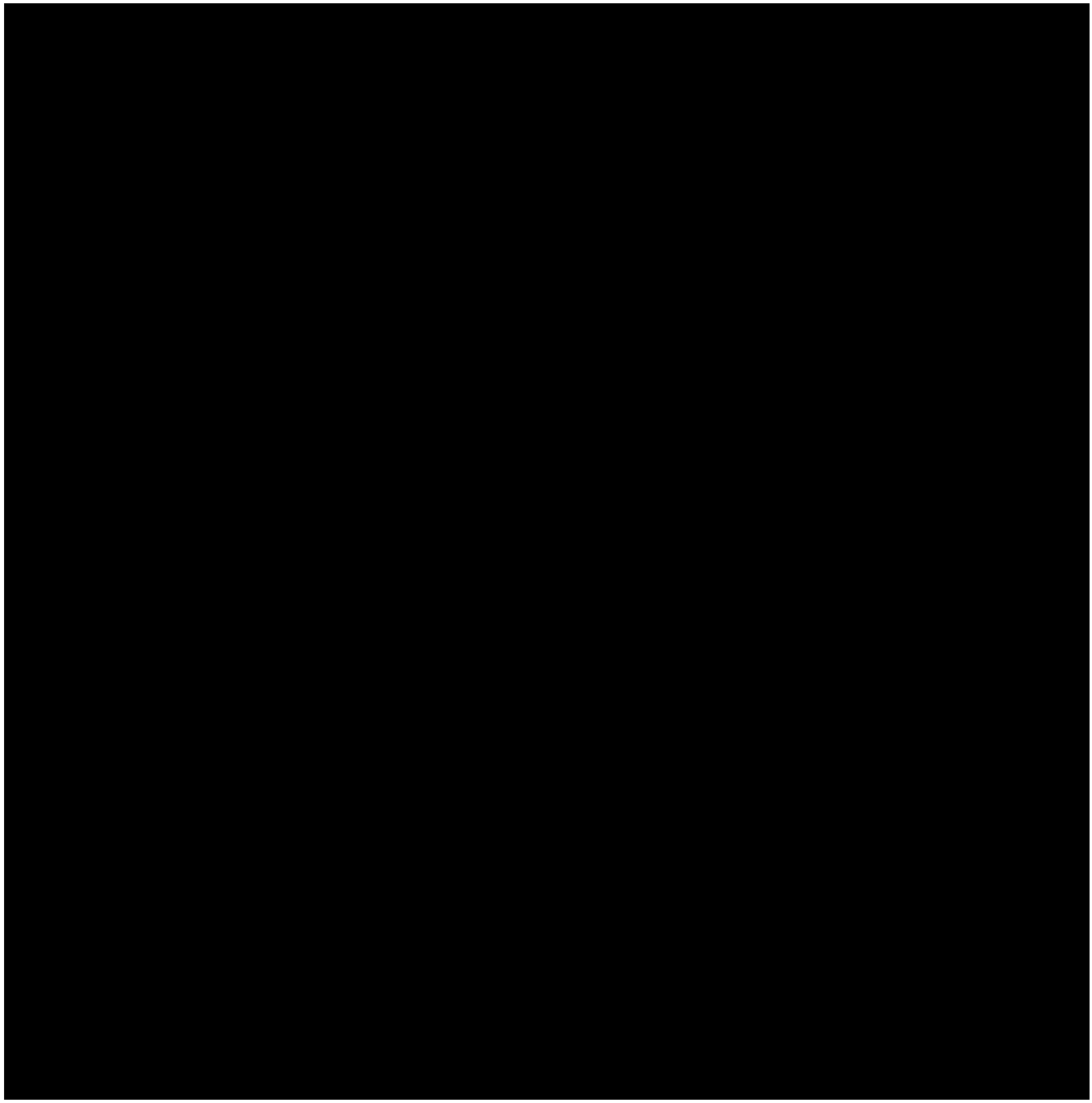


Figure 5-~~5~~1 Determination of sustained pain freedom from 2 to 24 hours after the initial dose

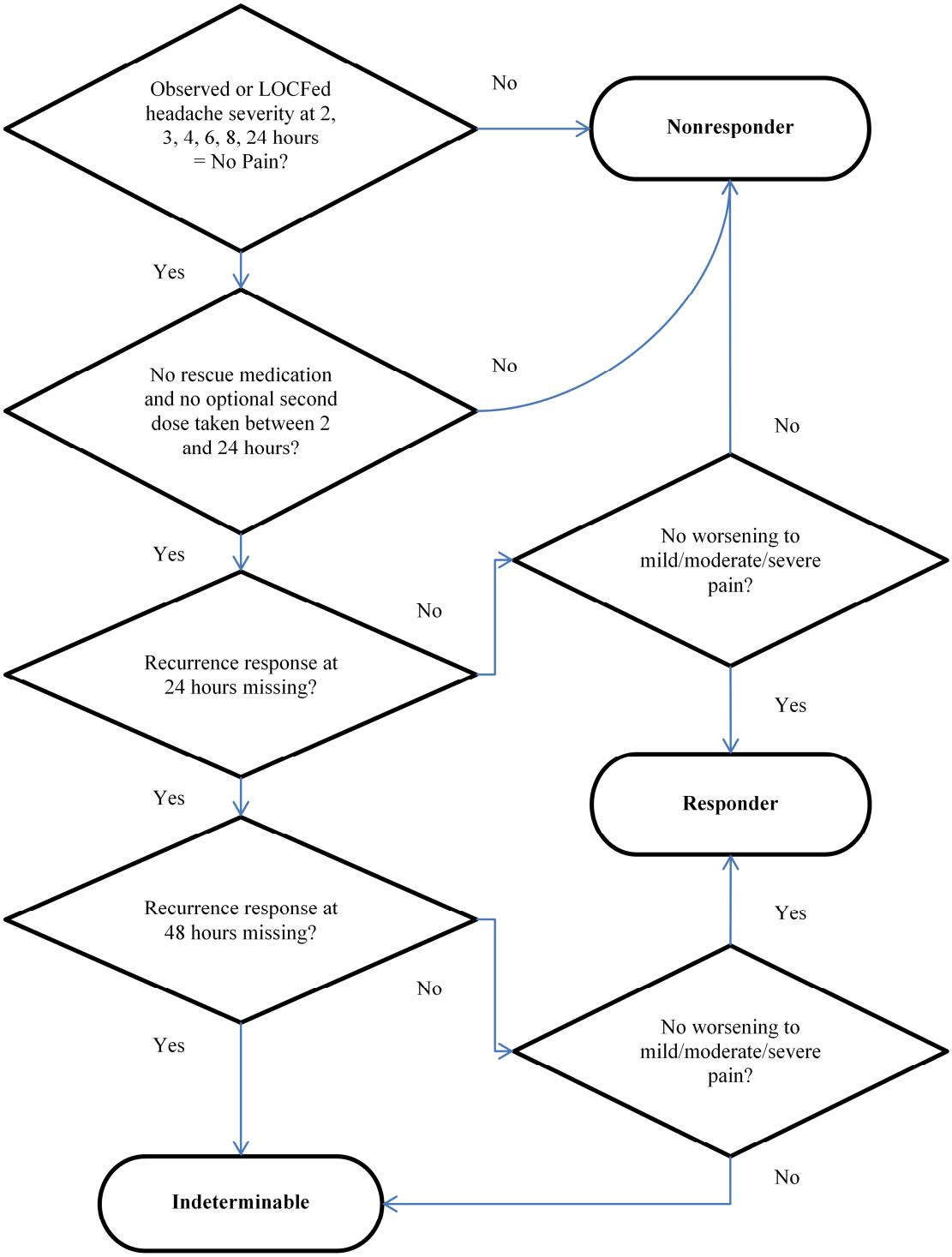


Figure 5-~~6~~7 Determination of sustained pain relief from 2 to 24 hours after the initial dose

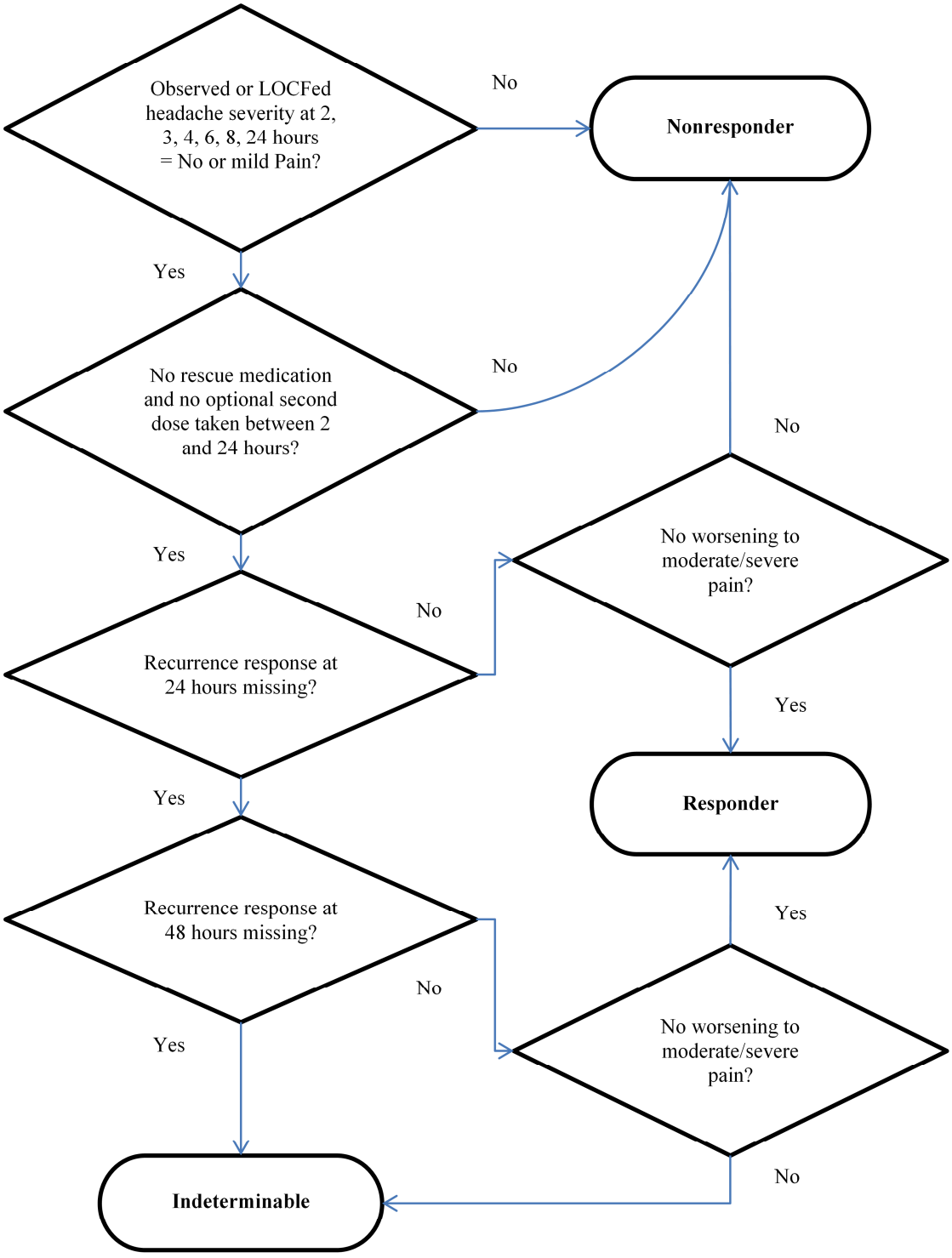


Figure 5-~~73~~ Determination of sustained pain freedom from 2 to 48 hours after the initial dose

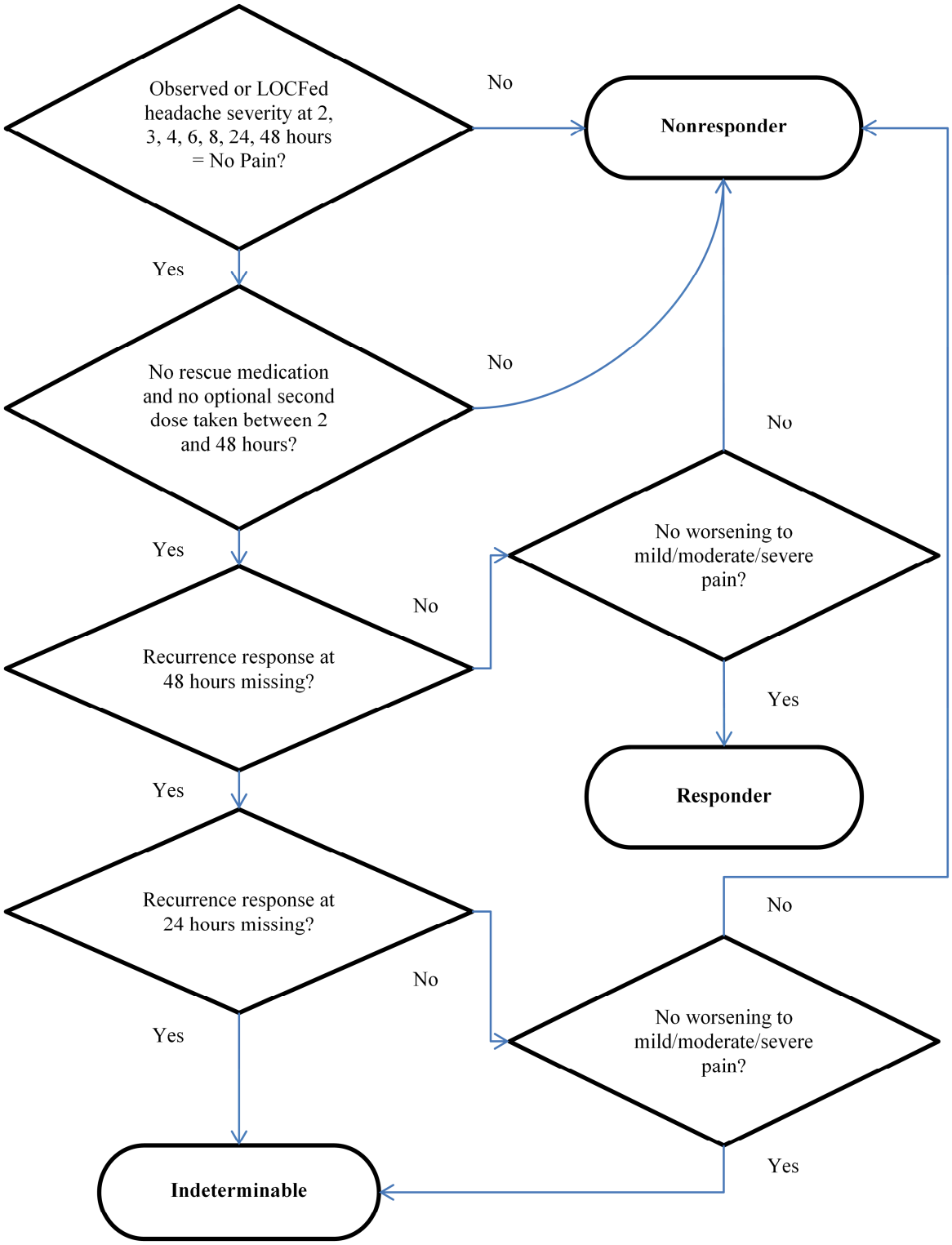
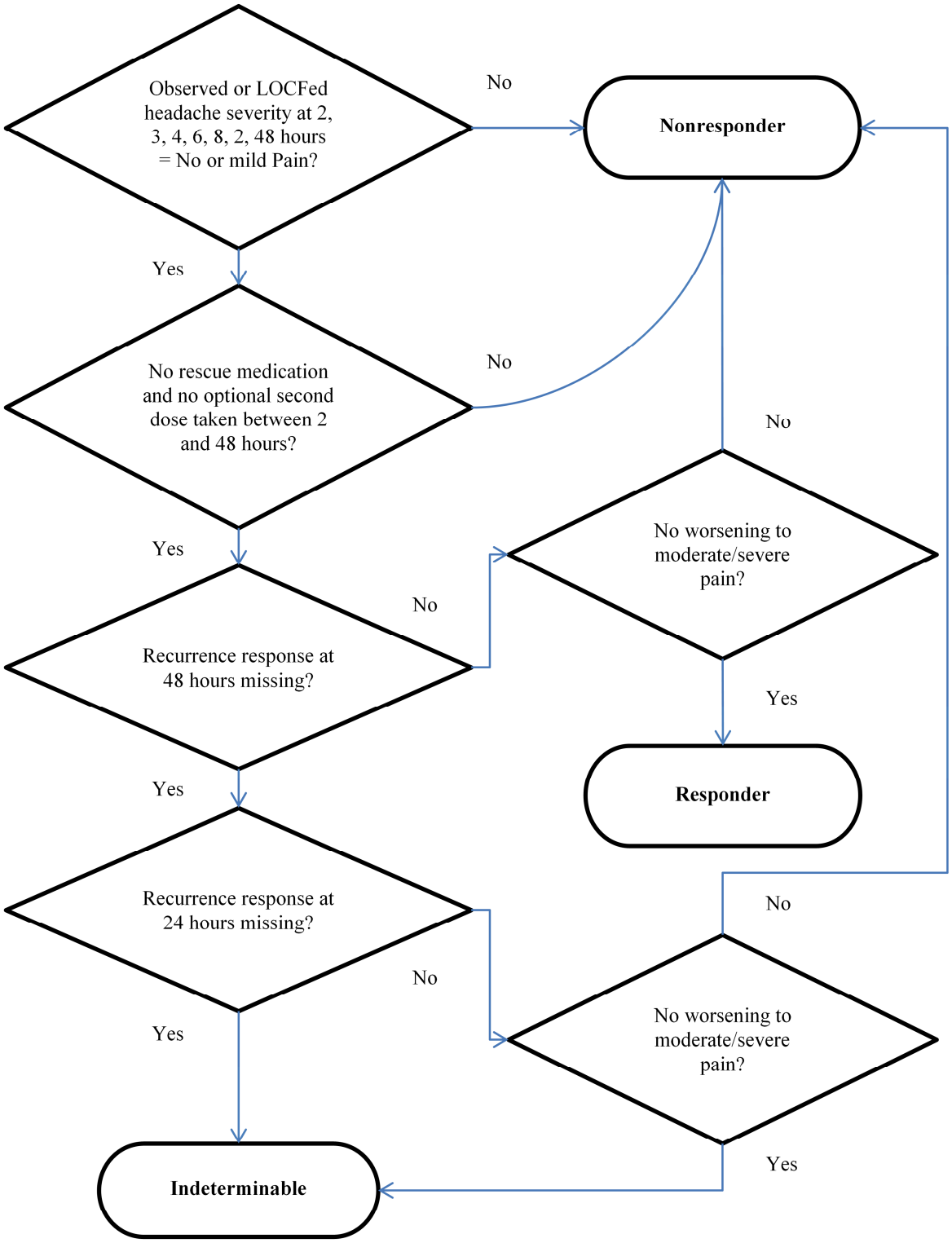


Figure 5-84 Determination of sustained pain relief from 2 to 48 hours after the initial dose



1.5.4 Table 5-14, US Analyses [redacted] (Pages 37-44)

Rationale: These tables have been amended to reflect the addition of 9 other efficacy endpoints.

The US Analyses and [redacted] tables now reads as follows:

Table 5-14 US Analyses

Endpoint	Description	Timing	Methodology
P1	Pain freedom (PF) at 2 hours after the initial dose, defined as a reduction in headache severity from moderate/severe at baseline to no pain, at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
P2	Absence of the most bothersome migraine-associated symptom (the most bothersome migraine-associated symptom will be identified at baseline for each participant) at 2 hours after the initial dose.	2 hours after the initial dose	Logistic regression model
S1	Pain relief (PR) at 2 hours after the initial dose, defined as the reduction of a moderate/severe migraine headache to a mild headache or to no headache, at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
S2	Sustained pain relief (SPR) from 2 to 24 hours after the initial dose, defined as pain relief with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a moderate/severe headache during the relevant number of hours after dosing with the IP	2 to 24 hours after the initial dose	Logistic regression model
S3	Sustained pain freedom (SPF) from 2 to 24 hours after the initial dose, defined as pain freedom with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a mild/moderate/severe headache during the relevant number of hours after dosing with the IP	2 to 24 hours after the initial dose	Logistic regression model
S4a	Absence of photophobia at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
S4b	Absence of phonophobia at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model

Endpoint	Description	Timing	Methodology
S4c	Absence of nausea at 2 hours after the initial dose	2 hours after the initial dose	Logistic regression model
[redacted]	[redacted]	[redacted]	[redacted]
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Endpoint	Description	Timing	Methodology
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Endpoint	Description	Timing	Methodology
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Endpoint	Description	Timing	Methodology
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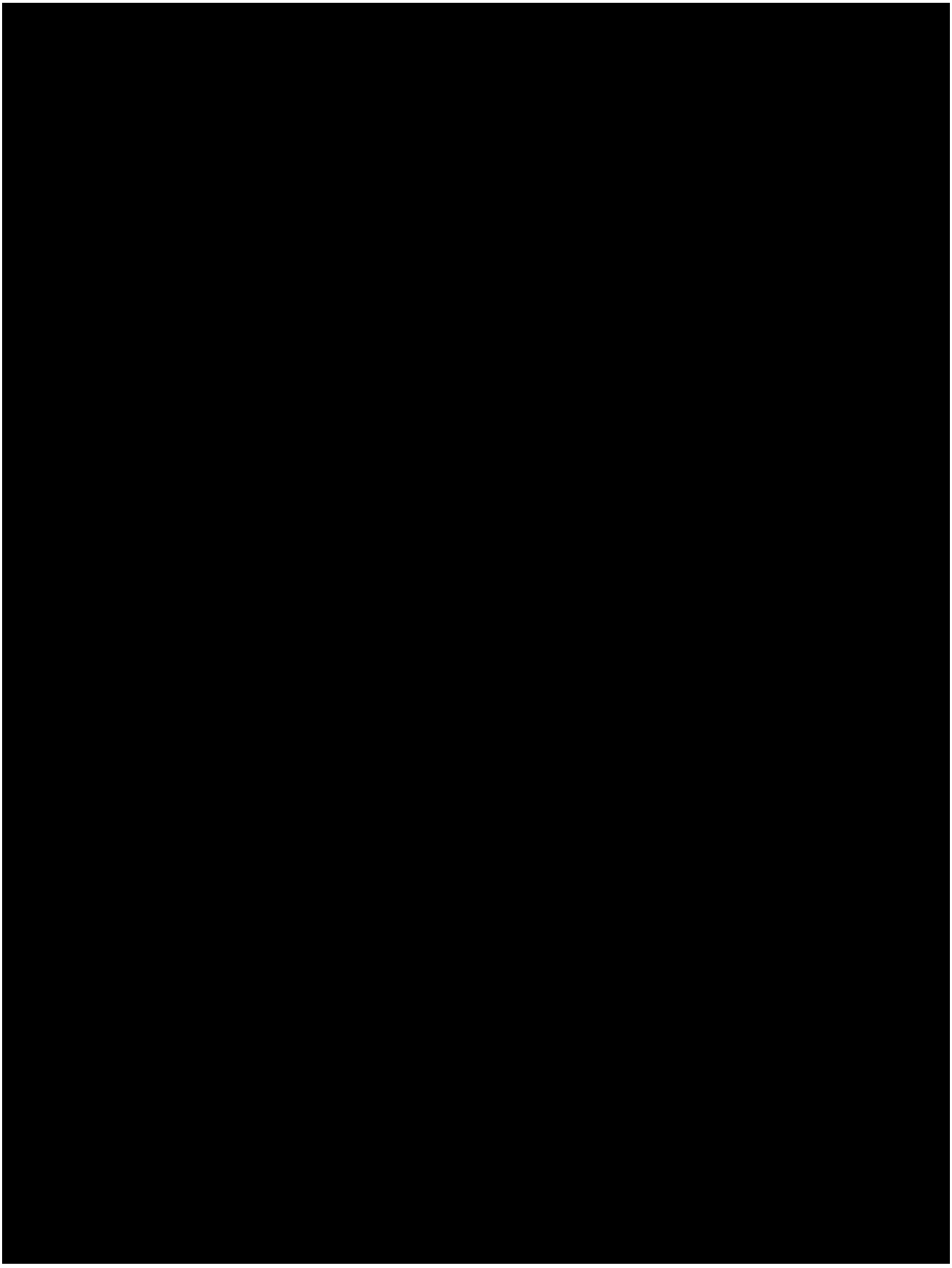
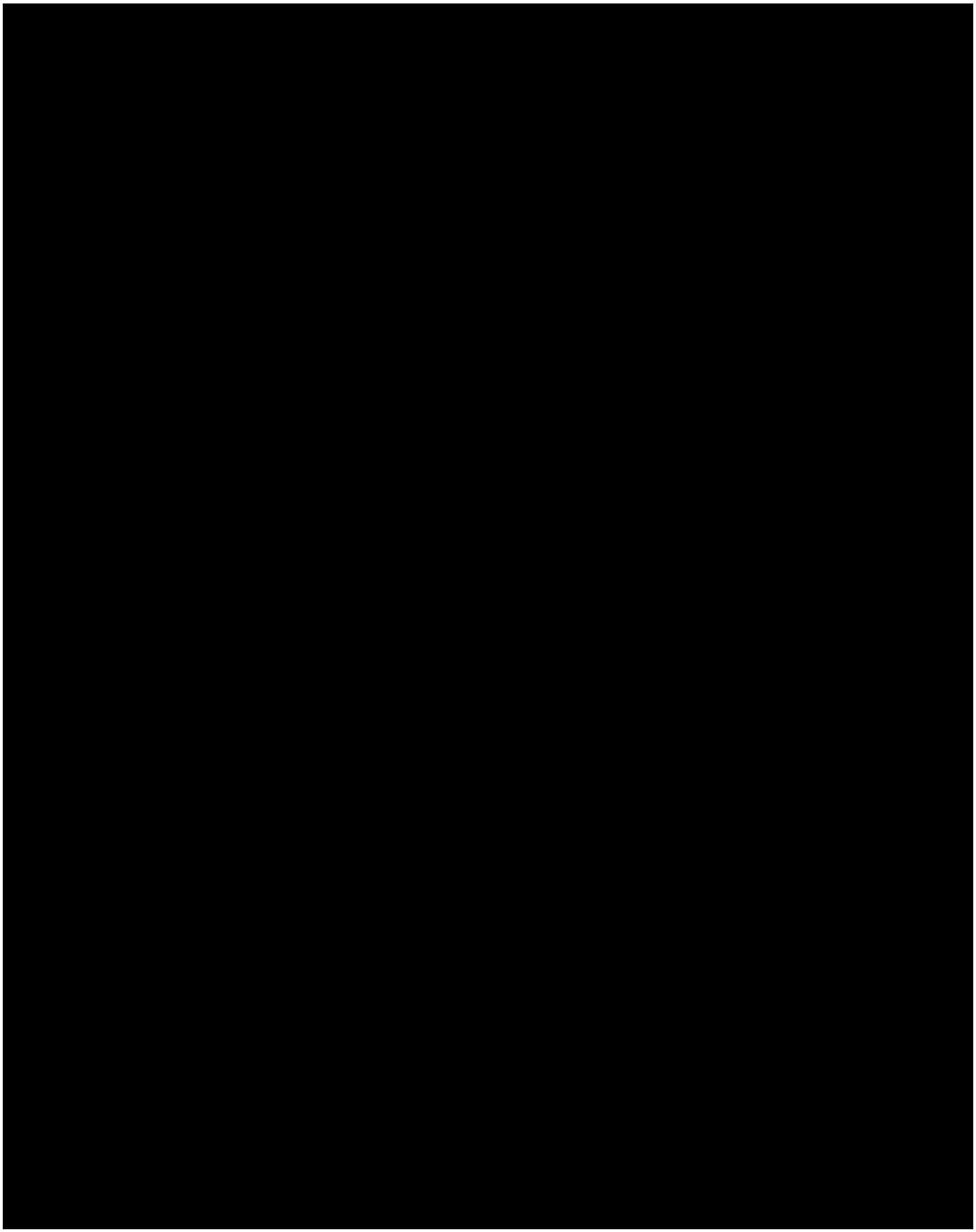
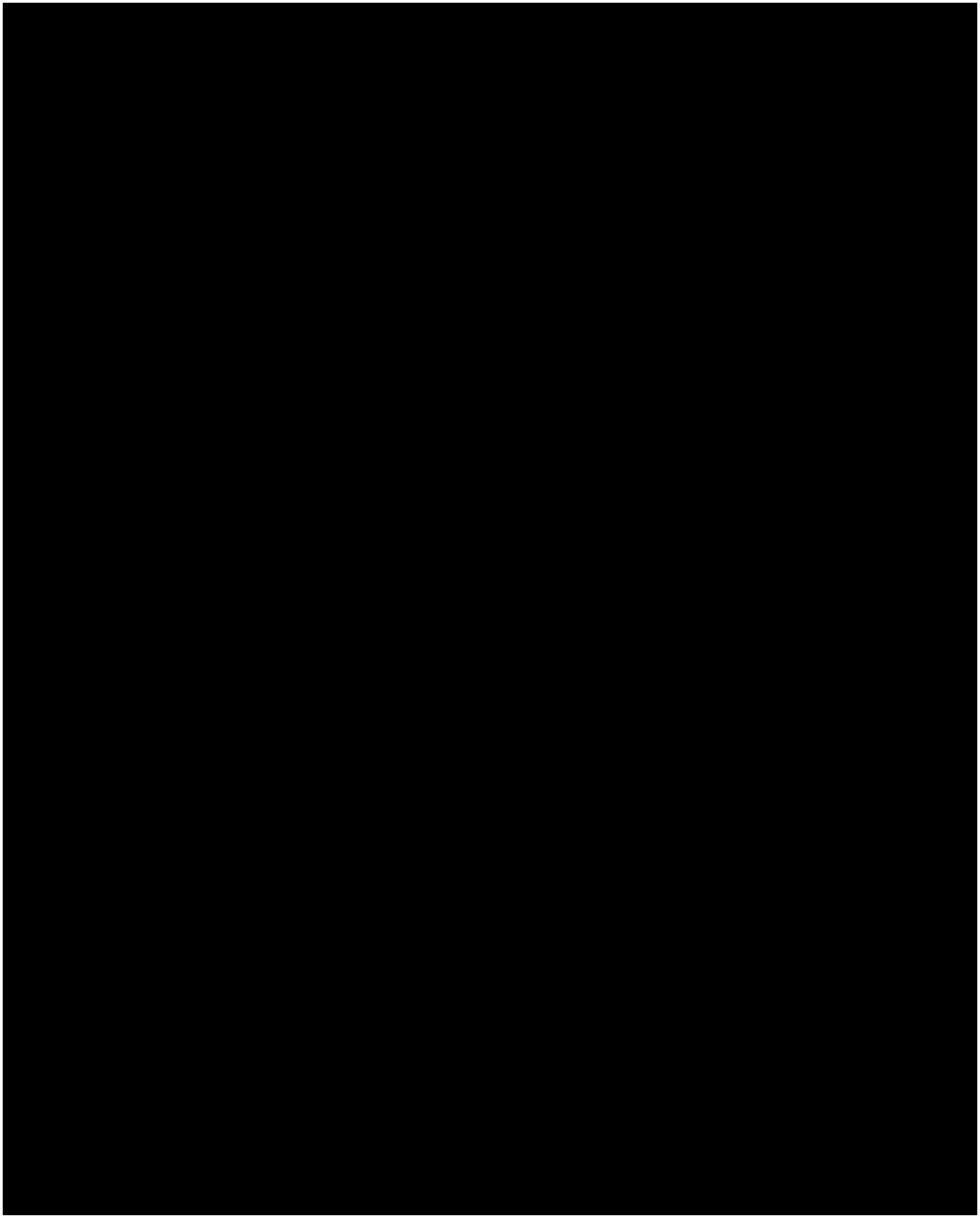
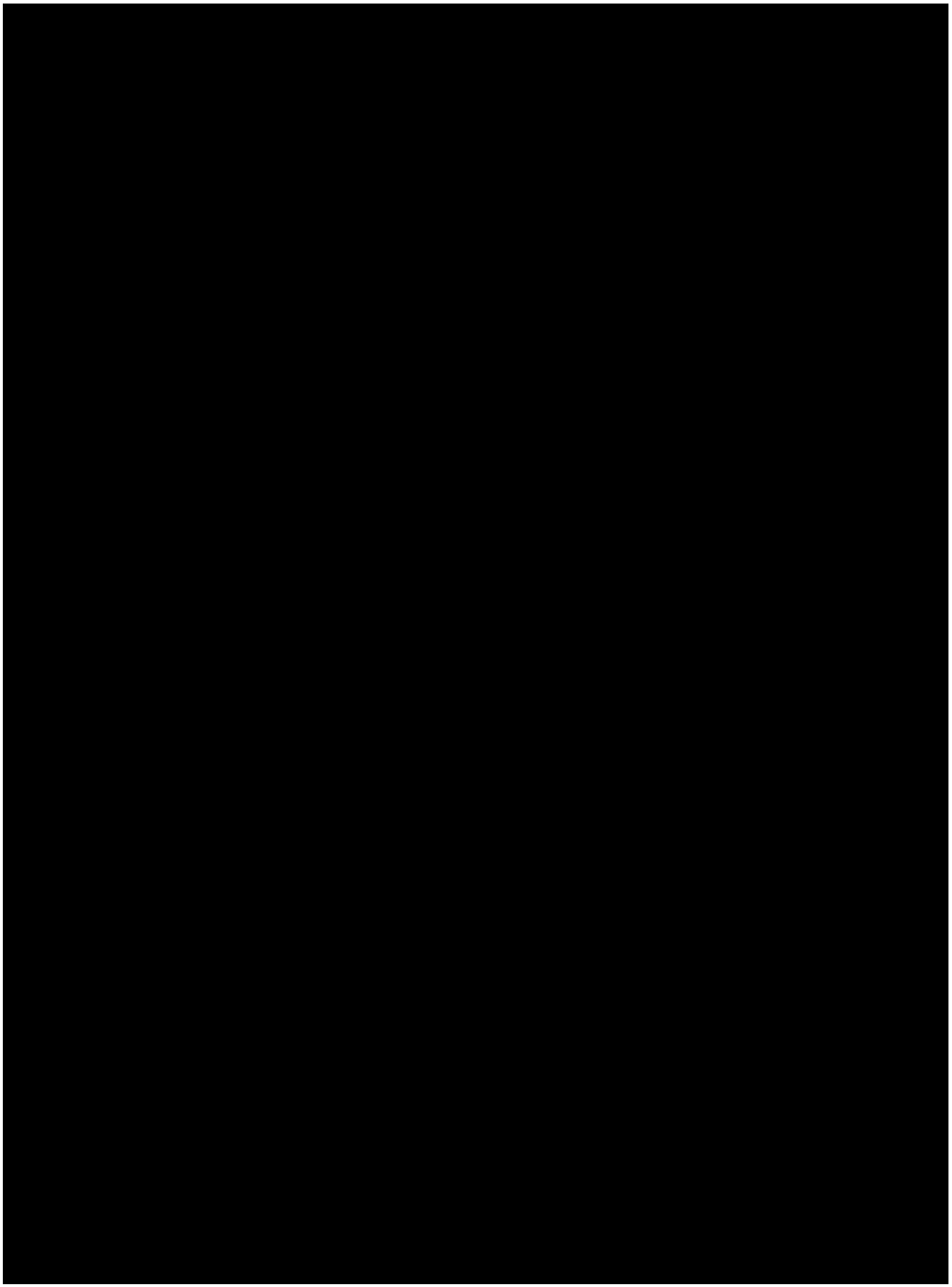








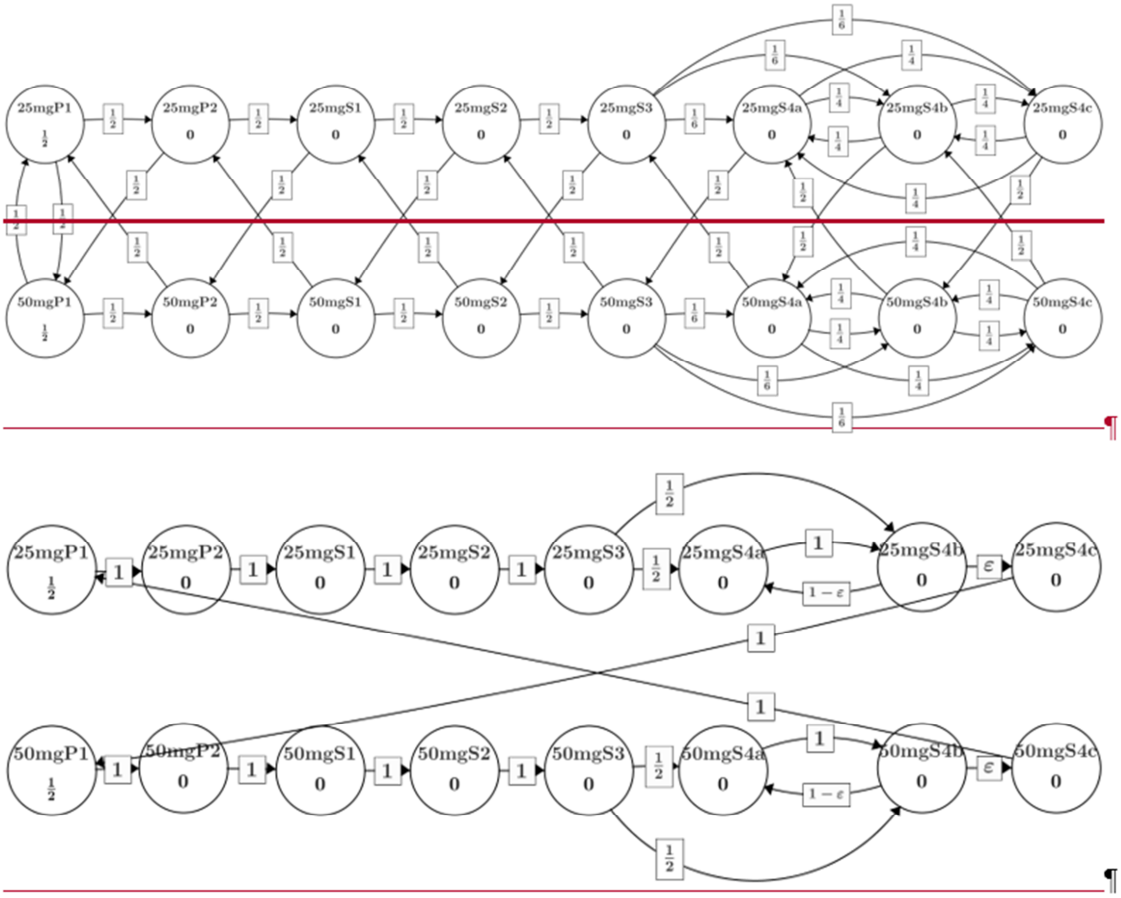
1.5.5 Section 5.1.1.3.4 Multiple Comparisons Procedure for Primary and Secondary Endpoints (Pages 46-48)

Rationale: This section has been modified to enhance the robustness of the testing procedure for efficacy at the ubrogepant 50 mg dose, in order to better reflect the relative clinical importance and likelihood of demonstration of effect for each endpoint.

The section now reads as follows:

A graphical approach by Bretz et al (2009) will be used to control the overall type I error rate for multiple comparisons across the ubrogepant doses and the primary and secondary efficacy endpoints. For the US analyses, the coprimary efficacy endpoints will serve as the gatekeepers of the secondary endpoints. [redacted]. The secondary endpoints will be tested in the same order as they appear in the list of secondary endpoints, except for the 2 ~~3~~ migraine-associated symptoms, photophobia and phonophobia, which will be treated at the same level to allow the recycling of weights among the 2 ~~3~~ symptom endpoints. Recycling of weights between the 2 doses from nausea to pain freedom is also allowed.

Figure 5-9~~5~~ Multiple Comparisons Procedure for the US



1.5.6 Section 5.1.1.4.1 Study Treatment Exposure and Compliance (Page 48)

Rationale: This section has been amended to add the summary of treatment exposure.

This section now reads as follows:

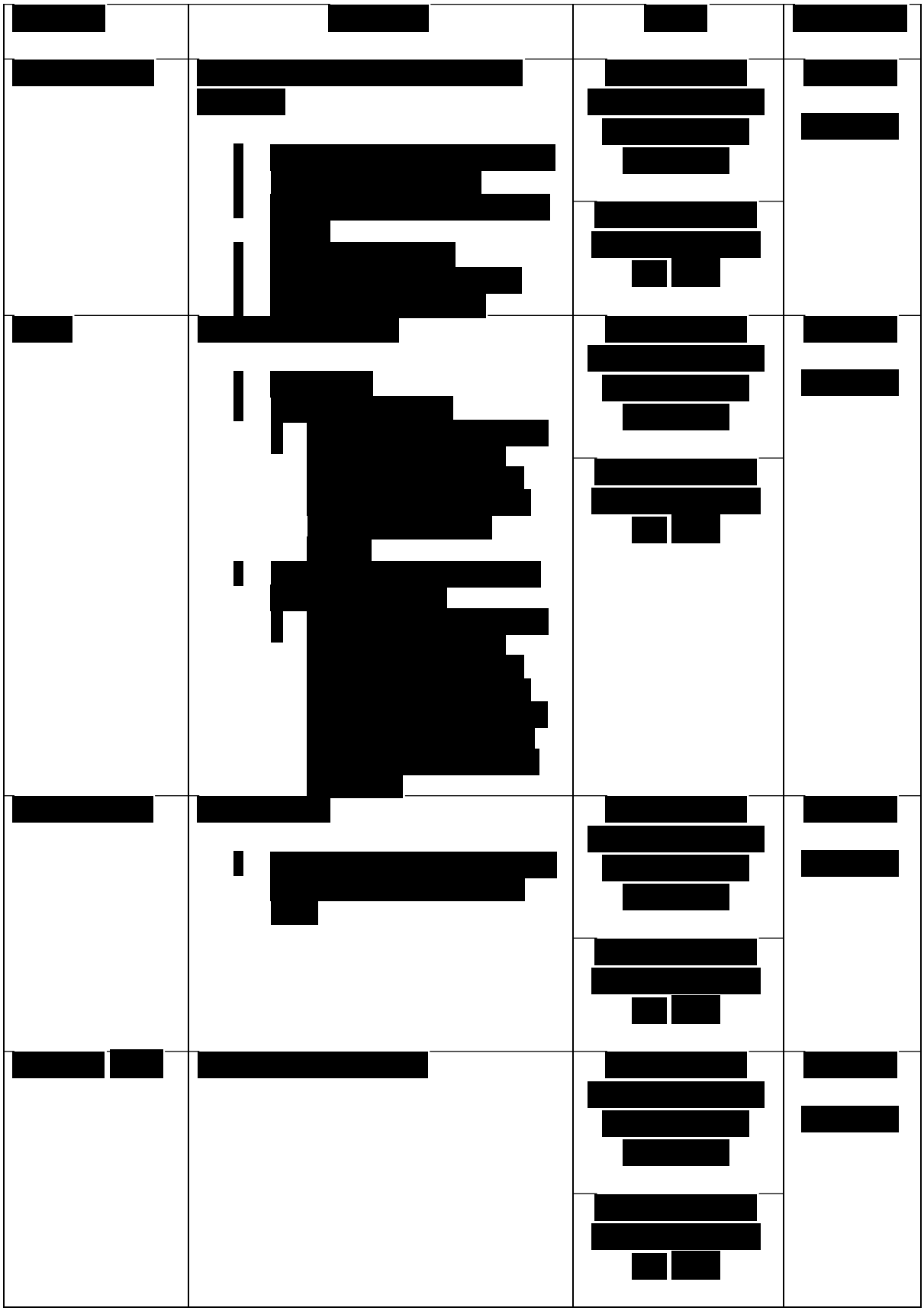
Study treatment exposure will be summarized and listed for the Safety Population.

The summary of treatment exposure will include the number and percentage of participants who took the initial dose only, the number and percentage of participants who took both the initial dose and the optional second dose, and the number and percentage of participants who took the PK dose for each treatment group.

The listing of treatment exposure will indicate whether the participant took the optional second dose and [redacted] in addition to the first dose.

Treatment compliance to the first dose of study medication will not be calculated as participants are only to take 1 tablet.

[redacted]



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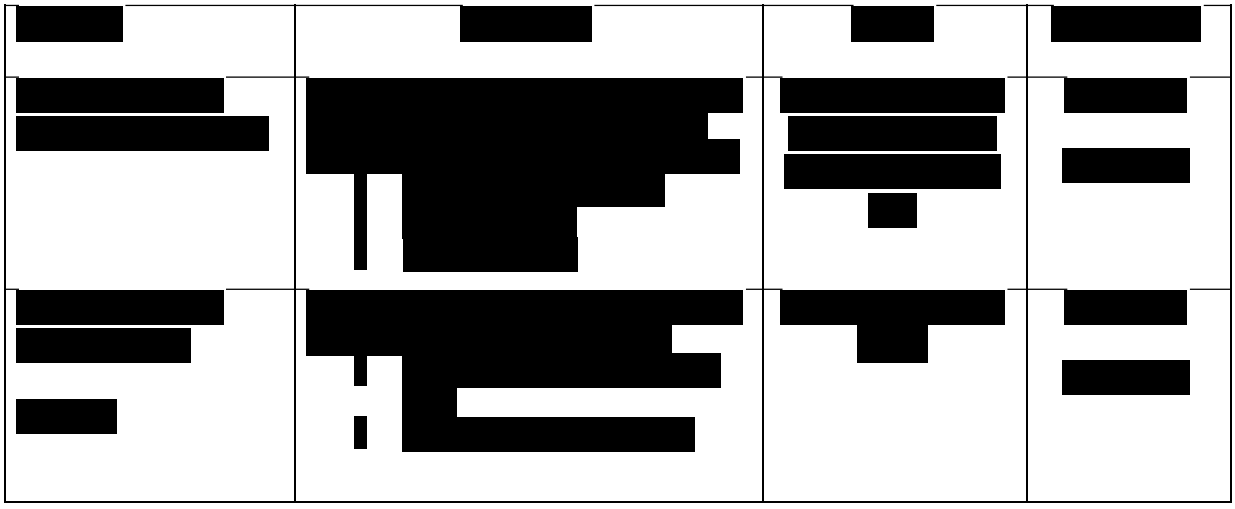

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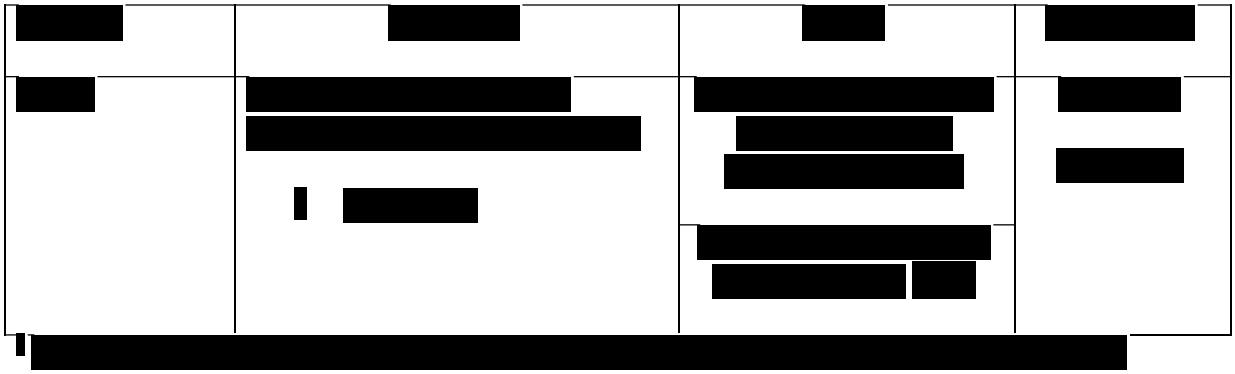


1.5.10 Section 5.1.1.5 Subgroup Analyses

The section now reads as follows:

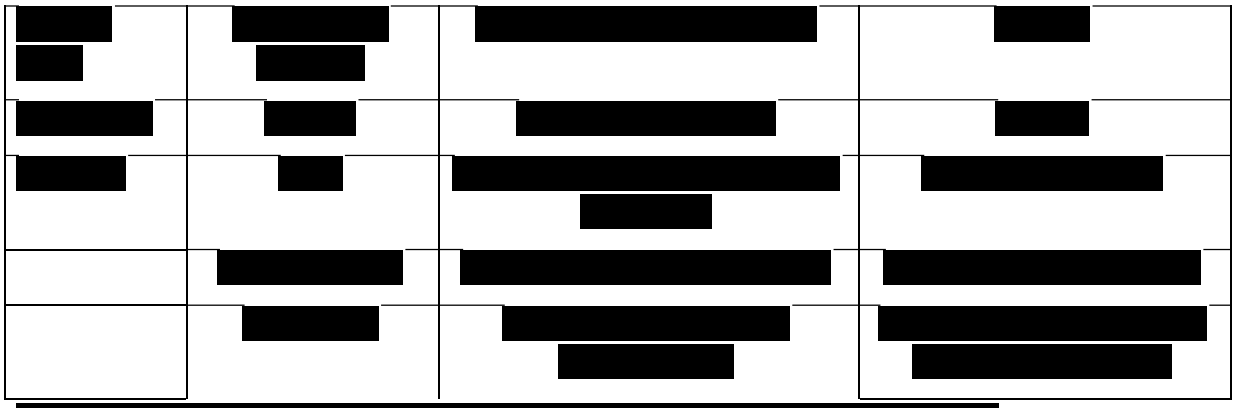
The following subgroup analyses will be conducted by historical triptan response. PF and absence of the most bothersome migraine-associated symptom at 2 hours after initial dose will be analyzed using similar models as the primary endpoints with the additional treatment group by historical triptan response interaction. Time to PF and absence of the most bothersome migraine-associated symptom within 2 hours after the initial dose will be analyzed by historical triptan response separately.

- PF at 2 hours after initial dose

- Absence of the most bothersome migraine-associated symptom at 2 hours after initial dose (US only)
- Time to PF within 48 hours after the initial dose
- Time to absence of the most bothersome migraine-associated symptom within 48 hours after the initial dose (US only)

[redacted]

[redacted]



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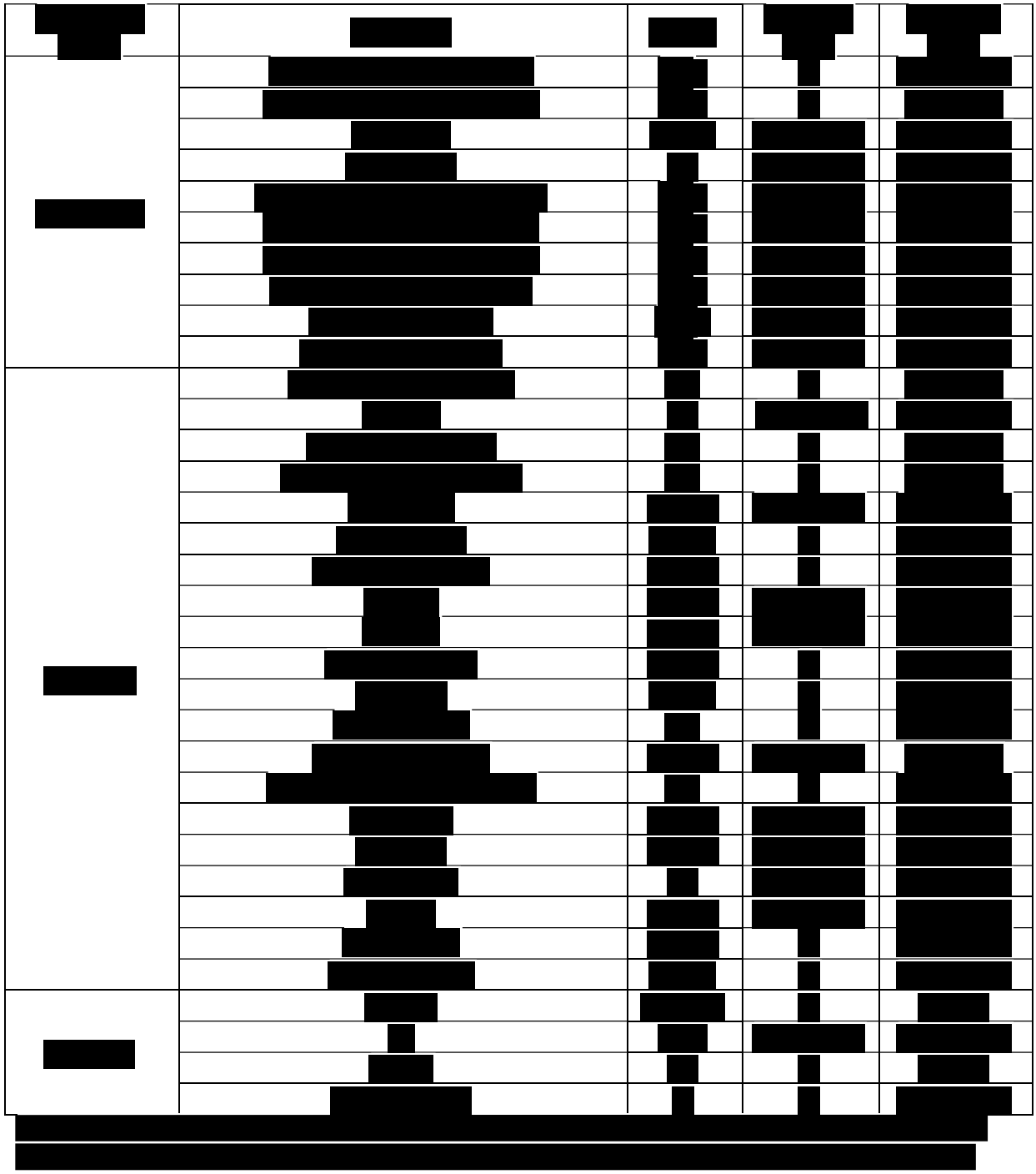

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