Study ID: UBR-MD-01

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 2 Date: 22 Jan 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: 2017-01-05

Amendment 1: 2017-05-17

Amendment 2: 2018-01-22

Protocol Number: UBR-MD-01 Amendment 3
Development Phase: 3
Product Name: Ubrogepant
Study Statistician: [Redacted]
Sponsor: Allergan, Inc.

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2. Table of Contents

1. Title Page ................................................................................................................................ 1

2. Table of Contents ..................................................................................................................... 2
   2.1 List of Tables .................................................................................................................. 3
   2.2 List of Figures ................................................................................................................ 5

3. List of Abbreviations and Definition of Terms ........................................................................ 6

4. Introduction................................................................................................................................ 8
   4.1 Study Design Summary ................................................................................................. 8
   4.2 Study Objectives and Endpoints .................................................................................... 9

5. Statistical Methodology and Study Endpoints ....................................................................... 18
   5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size ........ 18
      5.1.1 Statistical and Analytical Plans ........................................................................ 18
      5.1.1.1 Common Conventions ....................................................................... 18
      5.1.1.2 Demographics.................................................................................... 32
      5.1.1.3 Efficacy and .................................................................................... 36

5.2 Changes in the Conduct of the Study or Planned Analyses ................................................. 55
   5.2.1 Changes in the Conduct of the Study ........................................................................ 55
   5.2.2 Changes to Analyses Prior to Database Lock ...................................................... 55

6. Data Handling and Analysis Conventions ............................................................................. 56
   6.1 Study Treatment Conventions ...................................................................................... 56
      6.1.1 Analysis Days .................................................................................................. 56
      6.1.2 Missing/Incomplete Treatment End Date ......................................................... 56
   6.2 Analysis Visit Windows ...............................................................................................56
      6.2.1 Efficacy ............................................................................................................ 56
6.4 Imputed Value Listing Conventions ............................................................................. 64

7. References .............................................................................................................................. 65

2.1 List of Tables

Table 3-1 Abbreviations and Definitions of Terms ................................................................. 6
Table 4-1 Study Objectives and Corresponding Endpoints .................................................... 9
Table 5-1 Analysis Populations ............................................................................................. 18
Table 5-2 Statistical Methodology ........................................................................................ 19
Table 5-3 Missing Data Handling by Endpoint Type ............................................................ 21
Table 5-4 Analysis Population Summaries ........................................................................... 32
Table 5-5 Participant Disposition Summaries ....................................................................... 32
Table 5-6 Protocol Deviation Summary ................................................................................ 33
Table 5-7 Demographic Summaries ...................................................................................... 33
Table 5-8 Baseline Characteristics Summaries ..................................................................... 34
Table 5-9 Medical History Summary ...................................................................................... 34
Table 5-10  Migraine History Summary ................................................................. 35
Table 5-11  Medication Summaries ................................................................. 35
Table 5-12  Efficacy Assessments ................................................................. 36
Table 5-13  Efficacy Endpoint Baseline Definitions ........................................ 37
Table 5-14  US Analyses ............................................................................. 37
Table 5-15  EU Analyses ............................................................................. 41
Table 5-16  Multiple Comparisons Procedure Definitions for the US .......... 45
Table 5-27  Assumed Response Rates and Estimated Power for Primary and Secondary Efficacy Endpoints ........................................ 54
Table 6-1  Analysis Day Definitions ................................................................. 56
Table 6-2  Efficacy Analysis Visit Definitions ................................................. 56
## 2.2 List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-5</td>
<td>Determination of sustained pain freedom from 2 to 24 hours after the initial dose</td>
<td>28</td>
</tr>
<tr>
<td>5-6</td>
<td>Determination of sustained pain relief from 2 to 24 hours after the initial dose</td>
<td>29</td>
</tr>
<tr>
<td>5-7</td>
<td>Determination of sustained pain freedom from 2 to 48 hours after the initial dose</td>
<td>30</td>
</tr>
<tr>
<td>5-8</td>
<td>Determination of sustained pain relief from 2 to 48 hours after the initial dose</td>
<td>31</td>
</tr>
<tr>
<td>5-9</td>
<td>Multiple Comparisons Procedure for the US</td>
<td>45</td>
</tr>
</tbody>
</table>
### 3. List of Abbreviations and Definition of Terms

#### Table 3-1 Abbreviations and Definitions of Terms

<table>
<thead>
<tr>
<th>Abbreviation/Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALP</td>
<td>alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of covariance</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Columbia–Suicide Severity Rating Scale</td>
</tr>
<tr>
<td>CFB</td>
<td>change from baseline</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>DBS</td>
<td>dry blood spot</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram, electrocardiographic</td>
</tr>
<tr>
<td>EQ VAS</td>
<td>European Quality of Life Visual Analogue Scale</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>European Quality of Life 5 Dimensional – 5 Level</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDS</td>
<td>Functional Disability Scale</td>
</tr>
<tr>
<td>FWER</td>
<td>familywise error rate</td>
</tr>
<tr>
<td>HEOR</td>
<td>Health Economics and Outcomes Research</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IP</td>
<td>investigational product</td>
</tr>
<tr>
<td>IWRS</td>
<td>interactive web response system</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram(s)</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>LOCF</td>
<td>last observation carried forward</td>
</tr>
<tr>
<td>LS</td>
<td>least squares</td>
</tr>
<tr>
<td>m</td>
<td>meter(s)</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medication Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>milligrams</td>
</tr>
<tr>
<td>mITT</td>
<td>modified intent-to-treat</td>
</tr>
<tr>
<td>PCS</td>
<td>potentially clinically significant</td>
</tr>
<tr>
<td>PF</td>
<td>pain free</td>
</tr>
<tr>
<td>PGIC</td>
<td>Participant Global Impression of Change</td>
</tr>
<tr>
<td>PCS</td>
<td>potentially clinically significant</td>
</tr>
<tr>
<td>PO</td>
<td>Primary Objective</td>
</tr>
<tr>
<td>PR</td>
<td>pain relief</td>
</tr>
<tr>
<td>PT</td>
<td>preferred term</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate</td>
</tr>
<tr>
<td>QTcB</td>
<td>QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)</td>
</tr>
<tr>
<td>Abbreviation/Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
</tr>
<tr>
<td>QTcF</td>
<td>QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓)</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SAS</td>
<td>Statistical Analysis Software</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SI</td>
<td>Le Système International d’Unités (International System of Units)</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>SPF</td>
<td>sustained pain freedom</td>
</tr>
<tr>
<td>SPR</td>
<td>sustained pain relief</td>
</tr>
<tr>
<td>TBL</td>
<td>total bilirubin</td>
</tr>
<tr>
<td>TEAE</td>
<td>treatment-emergent adverse event</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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-01. Specifications of tables, figures, and data listings are contained in a separate document.

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 50 mg, or ubrogepant 100 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 50 mg, ubrogepant 100 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:* Participants will be randomized (1:1:1) to 1 of the following 3 treatment groups: placebo, ubrogepant 50 mg, or ubrogepant 100 mg.
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>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td><strong>Primary Efficacy Endpoints</strong></td>
</tr>
<tr>
<td>• [PO1] To compare the efficacy, safety, and tolerability of 2 doses of ubrogepant (50 and 100 mg) with placebo in participants with a single migraine attack</td>
<td>The coprimary efficacy parameters for the United States of America (US) are as follows:</td>
</tr>
<tr>
<td></td>
<td>• [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</td>
</tr>
<tr>
<td></td>
<td>• [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</td>
</tr>
<tr>
<td><strong>Secondary Efficacy Endpoints</strong></td>
<td>The secondary efficacy parameters for the US are:</td>
</tr>
</tbody>
</table>
| | • [S1] Pain relief (PR) at 2 hours after the initial dose, defined as the reduction of a
<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>moderate/severe migraine headache to a mild headache or to no headache, at 2 hours after the initial dose</td>
<td></td>
</tr>
<tr>
<td>• [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</td>
<td></td>
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<tr>
<td>• [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</td>
<td></td>
</tr>
<tr>
<td>• [S4a] Absence of photophobia at 2 hours after the initial dose</td>
<td></td>
</tr>
<tr>
<td>• [S4b] Absence of phonophobia at 2 hours after the initial dose</td>
<td></td>
</tr>
<tr>
<td>• [S4c] Absence of nausea at 2 hours after the initial dose</td>
<td></td>
</tr>
<tr>
<td>Objectives</td>
<td>Endpoints</td>
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<td>Objectives</td>
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</tbody>
</table>
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>
<thead>
<tr>
<th>Population</th>
<th>Definition</th>
<th>Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>All screened participants who signed informed consent</td>
<td>—</td>
</tr>
<tr>
<td>Intent-to-Treat (ITT)</td>
<td>All randomized participants.</td>
<td>Randomized assignment</td>
</tr>
<tr>
<td>Modified Intent-to-Treat (mITT)</td>
<td>All randomized participants who received at least 1 dose of study treatment, recorded a baseline migraine headache severity measurement, and had ≥ 1 postdose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint.</td>
<td>Randomized assignment</td>
</tr>
<tr>
<td>Safety</td>
<td>All participants who received ≥ 1 dose of study treatment</td>
<td>Actual received</td>
</tr>
</tbody>
</table>

5.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Placebo
- Ubrogepant 50 mg
- Ubrogepant 100 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

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Description</th>
</tr>
</thead>
</table>
| M1 Categorical counts | • Number of participants in individual categories  
  o Participants with ≥ 1 qualifying event counted once per individual category |
| M2 Categorical descriptives | • Number and percentage of participants in individual categories  
  o Participants with ≥ 1 qualifying event counted once per individual category  
  • N1 if proportion denominator ≠ number of participants in the population (standard percentage denominator)  
  o N1 = participants with non-missing baseline value |
| 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 |
| M8 Responder | • Categorical descriptives using proportions for responders and nonresponders  
  o Nonresponders include:  
    ▪ Participants who do not meet responder criteria  
  • N1 = all participants unless otherwise specified |
<table>
<thead>
<tr>
<th>Methodology</th>
<th>Description</th>
</tr>
</thead>
</table>
| M10 Logistic regression model | • Measures the relationship between the binary categorical dependent variable (responder or nonresponder) and independent variables  
  o Independent variables for initial dose:  
    ▪ treatment group (placebo, ubrogepant 50 mg, ubrogepant 100 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)  
  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.  
  For the analysis of the most bothersome symptom, the underlying symptom will be included as an additional covariate in the logistic regression model.  
  o 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  
  o Calculate two-sided p-values |
Methodology Description

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>
<thead>
<tr>
<th>Parameter type</th>
<th>Timing</th>
<th>Missing Data Handling</th>
</tr>
</thead>
</table>
| 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 |

A conservative approach will be 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.
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

- Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24 hours = No Pain?
  - Yes
  - No rescue medication and no optional second dose taken between 2 and 24 hours?
    - Yes
    - Recurrence response at 24 hours missing?
      - Yes
      - Recurrence response at 48 hours missing?
        - Yes
        - No worsening to mild/moderate/severe pain?
          - Yes
          - Responder
        - No
        - Indeterminable
      - No
      - No
    - No
    - No
  - No
  - No
  - No
  - No
  - No
Figure 5-6  Determination of sustained pain relief from 2 to 24 hours after the initial dose

- **Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24 hours = No or mild Pain?**
  - No → **Nonresponder**
  - Yes → **No rescue medication and no optional second dose taken between 2 and 24 hours?**
    - No → **No worsening to moderate/severe pain?**
      - Yes → **Responder**
      - No → **Indeterminable**
    - Yes → **Recurrence response at 24 hours missing?**
      - Yes → **Indeterminable**
      - No → **No worsening to moderate/severe pain?**
        - Yes → **Responder**
        - No → **Indeterminable**
Figure 5-7  
Determination of sustained pain freedom from 2 to 48 hours after the initial dose

1. Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24, 48 hours = No Pain?
   - No → Nonresponder
   - Yes → Next step

2. No rescue medication and no optional second dose taken between 2 and 48 hours?
   - No → Next step
   - Yes → Nonresponder

3. Recurrence response at 48 hours missing?
   - No → Next step
   - Yes → Indeterminable

4. No worsening to mild/moderate/severe pain?
   - Yes → Responder
   - No → Next step

5. Recurrence response at 24 hours missing?
   - No → Next step
   - Yes → Indeterminable

6. No worsening to mild/moderate/severe pain?
   - Yes → Responder
   - No → Next step

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

- Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24, 48 hours = No or mild Pain?
  - Yes → Responder
  - No → Nonresponder

- No rescue medication and no optional second dose taken between 2 and 48 hours?
  - Yes → Responder
  - No → Nonresponder

- Recurrence response at 48 hours missing?
  - Yes → Indeterminable
  - No → Nonresponder

- No worsening to moderate/severe pain?
  - Yes → Responder
  - No → Nonresponder

- Recurrence response at 24 hours missing?
  - Yes → Indeterminable
  - No → Nonresponder

- No worsening to moderate/severe pain?
  - Yes → Responder
  - No → Nonresponder
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>
<thead>
<tr>
<th>Table 5-4</th>
<th>Analysis Population Summaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Description</td>
</tr>
<tr>
<td>Screened Population</td>
<td>Distribution overall and within sites in total</td>
</tr>
<tr>
<td>ITT, mITT, and Safety populations</td>
<td>Distribution overall and within sites in total and by treatment group</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Table 5-5</th>
<th>Participant Disposition Summaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Description</td>
</tr>
<tr>
<td>Screening disposition(^1)</td>
<td>Distribution in the Screened Population in total</td>
</tr>
<tr>
<td>Double blind disposition(^1)</td>
<td>Distribution in the Safety Population and ITT Population in total and by treatment group</td>
</tr>
<tr>
<td>4 Week Safety Follow-up disposition(^1)</td>
<td>Distribution in the Safety Population and ITT Population in total and by treatment group</td>
</tr>
</tbody>
</table>

\(^1\) 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>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major protocol deviations</td>
<td>Distribution in the ITT Population in total and by treatment group</td>
<td>—</td>
<td>Categorical descriptives</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age (years) relative to informed consent date</td>
<td>Informed consent</td>
<td>Continuous descriptives</td>
</tr>
<tr>
<td>Age group</td>
<td>• &lt;20 • 20 to 29 • 30 to 39 • 40 to 49 • 50 to 59 • 60 to 69 • &gt;= 70</td>
<td>Informed consent</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td>Sex, race, and ethnicity</td>
<td>• eCRF categories • Race group o White o Non-white</td>
<td>Screening Period</td>
<td>Categorical descriptives</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong> 1</td>
<td>• Height (m)</td>
<td>Latest assessment in Screening Period</td>
<td>Continuous descriptives</td>
</tr>
<tr>
<td></td>
<td>• Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Body mass index (BMI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Weight (kg) / height (m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomization strata</strong>      2</td>
<td>• Previous response to triptans (Triptan Responder, Triptan Insufficient Responder, Triptan Naïve)</td>
<td>Randomization date</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td></td>
<td>• Current use of prophylactic concomitant medication for migraine (Yes, No)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline efficacy</strong></td>
<td>Endpoints and timing fully described in Section 5.1.1.3</td>
<td>Predose</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td></td>
<td>• migraine headache severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• migraine-associated symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• most bothersome migraine-associated symptom by symptom</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Summary for mITT Population only</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular risk</strong></td>
<td>• Cardiovascular risk factor subgroup (low risk, moderate risk, high risk)</td>
<td>Randomization date</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td></td>
<td>Summary for Safety Population only</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical history</strong> 1</td>
<td>Abnormalities and surgeries occurring before the Screening Visit</td>
<td>Screening Period</td>
<td>Categorical descriptives</td>
</tr>
</tbody>
</table>

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  Migraine History Summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine Diagnosis</td>
<td>With Aura, Without Aura, Both</td>
<td>Screening Period</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td>Previous Prophylaxis Migraine Treatment</td>
<td>Yes or No</td>
<td>Screening Period</td>
<td>Categorical descriptives</td>
</tr>
</tbody>
</table>
| Acute Migraine Treatment                 | Categorize as Yes or No, and subcategorize the Yes by:  
|                                          |  • Triptan                                       | Screening Period      | Categorical descriptives|
|                                          |  • Ergot or Ergot Combinations                   |                       |                         |
|                                          |  • NSAID                                         |                       |                         |
|                                          |  • Opiate or Opiate Combination                   |                       |                         |
|                                          |  • Antiemetic Agent                               |                       |                         |
|                                          |  • Barbiturates                                   |                       |                         |
|                                          |  • Other                                         |                       |                         |
| Migraine Disorder Duration               | 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior medications</td>
<td>Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date</td>
<td>Screening Period</td>
<td>Categorical descriptives</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date</td>
<td>Treatment Period</td>
<td>Categorical descriptives</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Assessment/Term</th>
<th>Description</th>
</tr>
</thead>
</table>
| Rating of Headache Severity | 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 | 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 | 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 | Absence or presence of migraine-associated symptoms: photophobia, phonophobia, nausea, and vomiting  
  - Completed by the participant in e-diary |

1 Participant efficacy parameters will be listed.
Baseline assessments for applicable efficacy endpoints are defined as follows:

### Table 5-13  Efficacy Endpoint Baseline Definitions

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline rating of headache severity</td>
<td>Headache severity rating (Moderate, Severe)</td>
<td>pre-dose</td>
</tr>
<tr>
<td>Baseline migraine-associated symptom</td>
<td>Migraine-associated symptom</td>
<td>pre-dose</td>
</tr>
<tr>
<td></td>
<td>• Photophobia (Yes, No)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Phonophobia (Yes, No)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Nausea (Yes, No)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vomiting (Yes, No)</td>
<td></td>
</tr>
</tbody>
</table>

### 5.1.1.3.1  Endpoints for US

The efficacy endpoints for the United States analyses are described as follows:

### Table 5-14  US Analyses

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>P2</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S1</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S2</td>
<td>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</td>
<td>2 to 24 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S3</td>
<td>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</td>
<td>2 to 24 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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<tr>
<td>S4a</td>
<td>Absence of photophobia at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S4b</td>
<td>Absence of phonophobia at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S4c</td>
<td>Absence of nausea at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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...
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
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...
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
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<tr>
<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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</tbody>
</table>
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 50 mg/50 mg, ubrogepant 50 mg/placebo, ubrogepant 100 mg/100 mg, ubrogepant 100 mg/placebo). The denominator is the number of participants who took the optional second dose.

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. The secondary endpoints will be tested in the same order as they appear in the list of secondary endpoints, except for the 3 migraine-associated symptoms which will be treated at the same level to allow the recycling of weights among the 3 symptom endpoints. Recycling of weights between the 2 doses 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 \( \alpha \), 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.

![Multiple Comparisons Procedure for the US](image)

### Table 5-16 Multiple Comparisons Procedure Definitions for the US

<table>
<thead>
<tr>
<th>Circle</th>
<th>Alternative Hypothesis</th>
<th>Objective</th>
<th>Weight</th>
<th>Local Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>50mgP1</td>
<td>Primary Efficacy Endpoint 1 for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>1/2</td>
<td>( \alpha*(1/2) = \alpha/2 )</td>
</tr>
<tr>
<td>50mgP2</td>
<td>Primary Efficacy Endpoint 2 for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>( \alpha*0 = 0 )</td>
</tr>
<tr>
<td>50mgS1</td>
<td>Secondary Efficacy Endpoint 1 for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>50mgS2</td>
<td>Secondary Efficacy Endpoint 2 for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>50mgS3</td>
<td>Secondary Efficacy Endpoint 3 for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>50mgS4a</td>
<td>Secondary Efficacy Endpoint 4a for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>50mgS4b</td>
<td>Secondary Efficacy Endpoint 4b for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>50mgS4c</td>
<td>Secondary Efficacy Endpoint 4c for 50 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgP1</td>
<td>Primary Efficacy Endpoint 1 for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>1/2</td>
<td>$\alpha*(1/2) = \alpha/2$</td>
</tr>
<tr>
<td>100mgP2</td>
<td>Primary Efficacy Endpoint 2 for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS1</td>
<td>Secondary Efficacy Endpoint 1 for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS2</td>
<td>Secondary Efficacy Endpoint 2 for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS3</td>
<td>Secondary Efficacy Endpoint 3 for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS4a</td>
<td>Secondary Efficacy Endpoint 4a for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS4b</td>
<td>Secondary Efficacy Endpoint 4b for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
<tr>
<td>100mgS4c</td>
<td>Secondary Efficacy Endpoint 4c for 100 mg ubrogepant is significantly different from placebo</td>
<td>PO1</td>
<td>0</td>
<td>$\alpha*0 = 0$</td>
</tr>
</tbody>
</table>
5.1.1.4.1 Study Treatment Exposure and Compliance

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

A summary of treatment compliance to the first dose of study medication in terms of the number and percentage of participants who took 2 tablets instead of only 1 tablet will be provided by treatment group.

The listing of treatment exposure will indicate whether the participant took the optional second dose and PK dose in addition to the first dose.
### 5.1.1.5 Subgroup Analyses

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.
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>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Day</td>
<td>Relative to treatment start date</td>
</tr>
<tr>
<td></td>
<td>If analysis date ≥ treatment start date:</td>
</tr>
<tr>
<td></td>
<td>• Day = analysis date − treatment start date + 1</td>
</tr>
<tr>
<td></td>
<td>o Day 1 = treatment start date</td>
</tr>
<tr>
<td></td>
<td>If analysis date &lt; treatment start date:</td>
</tr>
<tr>
<td></td>
<td>• Day = analysis date − treatment start date</td>
</tr>
<tr>
<td></td>
<td>o Day -1 = day before treatment start date</td>
</tr>
<tr>
<td></td>
<td>o There is no Day 0</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Analysis Phase</th>
<th>Analysis Visit (Derived)</th>
<th>Study Hour (eDiary)</th>
<th>Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>Baseline</td>
<td>Pre-dose</td>
<td>Based on nominal timepoints</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.5 hour post-dose</td>
<td>0.5 hour post-dose</td>
<td>recorded in eDiary</td>
</tr>
<tr>
<td></td>
<td>1 hour post-dose</td>
<td>1 hour post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.5 hours post-dose</td>
<td>1.5 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 hours post-dose</td>
<td>2 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 hours post-dose</td>
<td>3 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 hours post-dose</td>
<td>4 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 hours post-dose</td>
<td>6 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 hours post-dose</td>
<td>8 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 hours post-dose</td>
<td>24 hours post-dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48 hours post-dose</td>
<td>48 hours post-dose</td>
<td></td>
</tr>
<tr>
<td>[Redacted]</td>
<td>[Redacted]</td>
<td></td>
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</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]
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


UBR-MD-01

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: 5 Jan 2017
Amendment #1: 17 May 2017
Amendment #2: 22 Jan 2018

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1.0 AMENDMENT #2 TO STATISTICAL ANALYSIS PLAN FOR UBR-MD-01

1.1 INTRODUCTION
Amendment #2 specifies the following changes to the Statistical Analysis Plan (SAP) Amendment #1 for Study UBR-MD-01, dated 7 May 2017:

- Adding 3 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 the analysis of sustained efficacy endpoints
- Adding 3 endpoints in Table 5-14 US Analyses and
- Updating the Table 5-27 Assumed Response Rates and Estimated Power for Primary and Secondary Efficacy Endpoints
- 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 3 other efficacy endpoints to the list of other efficacy endpoints.
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.

This proportional odds model analysis now reads as follows:
1.5.3 Section 5.1.1.4, 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 5.1.1.3 and summarized as follows:

Table 5-3 Missing Data Handling by Endpoint Type

<table>
<thead>
<tr>
<th>Parameter type</th>
<th>Timing</th>
<th>Missing Data Handling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>Treatment Period</td>
<td>• If missing headache severity, migraine-associated symptoms, satisfaction with study medication, or functional disability scale at scheduled postdose time points, use LOCF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 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</td>
</tr>
</tbody>
</table>
A conservative approach will be 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 5-51  Determination of sustained pain freedom from 2 to 24 hours after the initial dose

- Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24 hours = No Pain?
  - Yes
    - No rescue medication and no optional second dose taken between 2 and 24 hours?
      - Yes
        - Recurrence response at 24 hours missing?
          - Yes
            - Indeterminable
          - No
            - No worsening to mild/moderate/severe pain?
              - Yes
                - Responder
              - No
                - No
              - Yes
                - No
                - No
      - No
        - No
      - No
        - No
          - Yes
            - No
            - No
              - No
              - No

- Indeterminable
Figure 5-62  Determination of sustained pain relief from 2 to 24 hours after the initial dose

- Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24 hours = No or mild Pain?
  - Yes
  - Recurrence response at 24 hours missing?
    - Yes
    - Recurrence response at 48 hours missing?
      - Yes
      - No worsening to moderate/severe pain?
        - Yes
      - No
      - Indeterminable
    - No
    - No worsening to moderate/severe pain?
      - Yes
      - No
    - No
  - No
  - No rescue medication and no optional second dose taken between 2 and 24 hours?
    - Yes
    - No
    - No
  - Nonresponder
- No
- Responder
**Figure 5-73** Determination of sustained pain freedom from 2 to 48 hours after the initial dose

- Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24, 48 hours = No Pain?
  - Yes
  - No
  - Nonresponder

- No rescue medication and no optional second dose taken between 2 and 48 hours?
  - Yes
  - No
  - Recurrence response at 48 hours missing?
    - Yes
    - No
    - Recurrence response at 24 hours missing?
      - Yes
      - No
      - No worsening to mild/moderate/severe pain?
        - Yes
        - Responder
        - No

- No worsening to mild/moderate/severe pain?
  - Yes
  - Indeterminable
  - No
Figure 5-84  Determination of sustained pain relief from 2 to 48 hours after the initial dose

Observed or LOCFed headache severity at 2, 3, 4, 6, 8, 24, 48 hours = No or mild Pain?

No

Yes

No rescue medication and no optional second dose taken between 2 and 48 hours?

No

Yes

Recurrence response at 48 hours missing?

No

Yes

Recurrence response at 24 hours missing?

No

Yes

No worsening to moderate/severe pain?

Responder

No

Yes

No worsening to moderate/severe pain?

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

**Rationale:** These tables have been amended to reflect adding 3 other efficacy endpoints.

The US Analyses [Table] now reads as follows:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Description</th>
<th>Timing</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>P2</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S1</td>
<td>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</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S2</td>
<td>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</td>
<td>2 to 24 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S3</td>
<td>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</td>
<td>2 to 24 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S4a</td>
<td>Absence of photophobia at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S4b</td>
<td>Absence of phonophobia at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>S4c</td>
<td>Absence of nausea at 2 hours after the initial dose</td>
<td>2 hours after the initial dose</td>
<td>Logistic regression model</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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<tr>
<td>Endpoint</td>
<td>Description</td>
<td>Timing</td>
<td>Methodology</td>
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<tr>
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</tr>
</tbody>
</table>

**UBR-MD-01 SAP Amendment #2 (Summary of Changes)**

22 Jan 2018
<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data 1</td>
<td>Data 2</td>
<td>Data 3</td>
<td>Data 4</td>
</tr>
<tr>
<td>Data 5</td>
<td>Data 6</td>
<td>Data 7</td>
<td>Data 8</td>
</tr>
<tr>
<td>Data 9</td>
<td>Data 10</td>
<td>Data 11</td>
<td>Data 12</td>
</tr>
</tbody>
</table>

*Note: The table content is not clearly visible and may need to be interpreted visually.*
1.5.8 Table 5-27, Assumed Response Rates and Estimated Power for Primary and Secondary Efficacy Endpoints (Pages 54-55)

**Rationale:** This table has been amended to update the power after multiplicity adjustment based on new sample size and new assumptions.

<table>
<thead>
<tr>
<th>h</th>
<th>PF</th>
<th>PR</th>
<th>SPF</th>
<th>SPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>2</td>
<td>E</td>
<td>F</td>
<td>G</td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>J</td>
<td>K</td>
<td>L</td>
</tr>
</tbody>
</table>

h = hours; PF = pain freedom; PR = pain relief; SPF = sustained pain freedom; SPR = sustained pain relief