Protocol C5301008

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ZAVEGEPANT INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE IN ASIAN ADULTS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 28 May 2025

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 21 Apr 2023	Original 22 Feb 2023	N/A	N/A
2 28 May 2025	Original 22 Feb 2023	• Clarified the CMH method for analysis of categorical efficacy endpoints to be Mantel-Haenszel risk estimation method. • Updated the definition of rescue medication within 24 hours post dose without consideration of analysis window and clarified the related time-to-event analysis. • Updated the safety analysis period for on-treatment period to include EOT visits with extended window in the analysis. • Clarified the analysis for AEs per team discussions. • Added subset analysis for co-primary and key secondary endpoints. • Deleted COVID-19 impact section. • Other minor updates for safety and baseline summaries.	• Section 5.2.2, Section 6.1, Section 6.2, Section 6.3 and Appendix 1. Clarified the CMH method for analysis of categorical efficacy endpoints percentage differences to be Mantel-Haenszel risk estimation method. • Section 5.2.3, Section 6.2.15 and Appendix 2.1. Updated the definition of rescue medication within 24 hours post dose without consideration of analysis window and clarified the related time-to-event analysis. • Section 5.2.4. Updated the safety analysis period for on-treatment period to include EOT visits with extended window in the analysis. • Section 3.5.1 and Section 6.6.1. Added TEAE definition, deleted treatment-related AEs for follow-up period, deleted summary for pre-treatment AEs, deleted AEs leading to discontinue of study intervention. Changed AESIs to other significant AEs and updated related AE types. • Section 6.4. Added subset analysis for co-primary and key secondary endpoints. • Deleted COVID-19 impact Original Section 5.2.5. • Section 3.4. Deleted ethnicity and racial designation from the baseline variables. • Section 5.3, Section 6.1.1.2 and Section 6.1.2.2. Updated the multiple imputation number from 20 to 30. • Section 6.1.1.1. Deleted the by country/region results from the main analysis of co-primary endpoints. • Section 6.2.14. Deleted the analysis for rescue medication use through 48 hours post dose. • Section 6.5.1.4. Added a separate summary table for medical history of hypertension. • Section 6.5.1.5. Updated the summary of non-study medications by PT only.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
			• Section 6.6.2.1. Deleted laboratory test toxicity grade shift summary. • Section 6.6.2.2. Deleted CI for LFT elevation summary and deleted LFT ULN shifts from baseline to worst elevation. • Section 6.6.3. Added summary table for vital signs for subgroup of participants with medical history of hypertension. • Section 6.6.5. Added summary table for C-SSRS. • Appendix 3.1. Updated AE terms for potential drug abuse AEs.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5301008.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable

2.2. Study Objectives, Endpoints, and Estimands

Type	Objective	Endpoint	Estimand
	Primary:	**Primary:**	**Primary:**
Efficacy	• To compare the efficacy of zavegepant with placebo in the acute treatment of migraine.	The following co-primary endpoints will be tested: • Percentage of participants with a pain intensity of none (pain freedom) at 2 hours postdose.	Co-primary estimands: • The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or

Type	Objective	Endpoint	Estimand
			before 2 hours postdose will be regarded as a failure.
		• Percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	Secondary:	**Secondary:**	**Secondary:**
	Key Secondary:	**Key Secondary:**	**Key Secondary:**
Efficacy	• To compare zavegepant with placebo for measures of early pain relief.	• Percentage of participants with a pain intensity of none or mild at 15 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
		• Percentage of participants with a pain intensity of none or mild at 30 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at

Type	Objective	Endpoint	Estimand
			or before 30 minutes postdose will be regarded as a failure.
		• Percentage of participants with a pain intensity of none or mild at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
Efficacy	• To compare zavegepant with placebo for return to normal function.	• Percentage of participants with a functional disability level of normal at 2 hours postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
Efficacy	• To compare zavegepant with placebo for measures of sustained pain relief.	• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.

Type	Objective	Endpoint	Estimand
		• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
Efficacy	• To compare zavegepant with placebo for measures of early return to normal function.	• Percentage of participants with a functional disability level of normal at 30 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 30 minutes postdose will be regarded as a failure.
		• Percentage of participants with a functional disability level of normal at 60 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.

Type	Objective	Endpoint	Estimand
	Other Secondary:	**Other Secondary:**	**Other Secondary:**
Efficacy	• To compare zavegepant with placebo for freedom from individual non-headache associated symptoms of migraine.	• Percentage of participants with phonophobia absent at 2 hours postdose, evaluated for participants with phonophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with phonophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had phonophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
		• Percentage of participants with photophobia absent at 2 hours postdose, evaluated for participants with photophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with photophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had photophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
		• Percentage of participants with nausea absent at 2 hours postdose, evaluated for participants with nausea present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with nausea absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had nausea at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.

Type	Objective	Endpoint	Estimand
Efficacy	• To compare zavegepant with placebo for additional measures of sustained efficacy.	• Percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.
		• Percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
		• Percentage of participants with pain relapse (any pain intensity above 'none') at any time point after 2 hours postdose, evaluated for participants with pain freedom at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of mild, moderate, or severe at any time point after 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had pain freedom at 2 hours postdose. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
Efficacy	• To compare zavegepant	• Percentage of participants taking	• The estimand is the treatment effect of zavegepant relative to placebo in

Type	Objective	Endpoint	Estimand
	with placebo for rescue medication use.	rescue medication within 24 hours postdose.	terms of the difference in percentage of participants taking rescue medication within 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. No relevant intercurrent event is considered since taking rescue medication is the analysis objective.
Efficacy	• To further compare zavegepant with placebo for early pain relief.	• Percentage of participants with a pain intensity of none or mild at 60 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.
Efficacy	• To further compare zavegepant with placebo for early return to normal function.	• Percentage of participants with a functional disability level of normal at 15 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
Safety	• To evaluate the safety and tolerability of zavegepant in	• Number and percentage of participants with AEs of moderate or severe intensity, SAEs, local irritation AEs, and	• Not applicable.

Type	Objective	Endpoint	Estimand
	the acute treatment of migraine.	grade 3 or 4 laboratory test abnormalities.	
	Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
Efficacy	• To evaluate the time course of zavegepant efficacy vs placebo.	• Percentage of responders at each of the assessed time points (15, 30, 45, 60, 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours) for each of the primary and secondary endpoints described above that assess a specific time point.	• As described above for each primary and secondary endpoint, using the applicable time point.
Efficacy	• To estimate zavegepant relative to placebo for the PGIC ratings.	• Percentage of participants with the overall status improvement at 30 minutes, 60 minutes, 2 hours and 24 hours postdose based on the total score of PGIC.	• Not applicable.

2.2.1. Primary Estimand(s)

The co-primary estimands of this study are using composite estimands. The estimands are defined according to the co-primary objectives and are in alignment with the co-primary endpoints. It includes the following 4+1 attributes:

- Treatment: Zavegepant and placebo;
- Population: All randomized participants with migraine headache of moderate or severe intensity who took study intervention;
- Variable: Percentage of participants with pain intensity of none (pain freedom) at 2 hours postdose and separately, the percentage of participants with an MBS reported on study before dosing that is absent at 2 hours postdose. The MBS before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, photophobia);

- Intercurrent event(s): Taking rescue medication at or before 2 hours postdose will be regarded as a failure.

- Population-level summary: Difference in percentages between zavegepant and placebo groups.

2.2.2. Secondary Estimand(s)

The secondary efficacy estimands of this study are using composite estimands. The estimands are defined according to the secondary efficacy objectives and are in alignment with the following secondary endpoints. It includes the following 4+1 attributes:

- Treatment: Zavegepant and placebo;

- Population: All randomized participants with migraine headache of moderate or severe intensity who took study intervention;

    - For the objective of evaluating return to normal function, phonophobia freedom, photophobia freedom, and nausea freedom at 2 hours postdose, the population will be participants defined above who had functional disability (mildly impaired, severely impaired, or requires bedrest), phonophobia presence, photophobia presence, and nausea presence, respectively, at the time of dosing.

    - For the objective of evaluating pain relapse, the population will be participants defined above who had pain freedom at 2 hours postdose.

- Variable:

    - Percentage of participants with a pain intensity of none or mild (pain relief) at 15 minutes, 30 minutes, 60 minutes, 2 hours postdose, at all time points from 2 to 24 hours postdose, at all time points from 2 to 48 hours postdose, respectively.

    - Percentage of participants with a functional disability level of normal at 15 minutes, 30 minutes, 60 minutes and 2 hours postdose, respectively.

    - Percentage of participants with phonophobia absence, with photophobia absence, with nausea absence at 2 hours postdose, respectively.

    - Percentage of participants with a pain intensity of none (pain freedom) at all time points from 2 to 24 hours postdose, at all time points from 2 to 48 hours postdose, respectively.

    - Percentage of participants with a pain intensity of mild, moderate, or severe (pain relapse) at any time point after 2 hours postdose.

- Intercurrent event(s): Taking rescue medication at or before the corresponding assessed time points as specified in the endpoints postdose will be regarded as a failure.

- Population-level summary: Difference in percentage of participants achieving the specific outcome at time points of interest between zavegepant and placebo groups.

The secondary efficacy estimand for objective of rescue medication use is defined by the following attributes:

- Treatment: Zavegepant and placebo;

- Population: All randomized participants with migraine headache of moderate or severe intensity who took study intervention;

- Variable: Percentage of participants taking rescue medication within 24 hours postdose;

- Intercurrent event(s): No relevant intercurrent event is considered since taking rescue medication is the analysis objective.

- Population-level summary: Difference in percentages between zavegepant and placebo groups.

2.2.3. Tertiary/Exploratory Estimand(s)

The exploratory estimand is a composite estimand. The estimand is defined according to the exploratory objectives and is in alignment with the following exploratory endpoints. It includes the following 4+1 attributes:

- Treatment: Zavegepant and placebo;

- Population: All randomized participants with migraine headache of moderate or severe intensity who took study intervention;

    - For the objective of evaluating return to normal function, phonophobia freedom, photophobia freedom, and nausea freedom at the specified time point postdose, the population will be participants defined above who had functional disability (mildly impaired, severely impaired, or requires bedrest), phonophobia presence, photophobia presence, and nausea presence, respectively, at the time of dosing.

- Variable:

    - Percentage of participants with a pain intensity of none (pain freedom) at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with an MBS reported before dosing that is absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.
- Percentage of participants with a pain intensity of none or mild (pain relief) at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.
- Percentage of participants with a functional disability level of normal at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.
- Percentage of participants with phonophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.
- Percentage of participants with photophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.
- Percentage of participants with nausea absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Intercurrent event(s): Taking rescue medication at or before the corresponding assessed time points as specified in the endpoints postdose will be regarded as a failure.
- Population-level summary: Difference in percentage of participants achieving the specific outcome at time points of interest between zavegepant and placebo groups.

2.3. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, single-attack, outpatient evaluation of the efficacy and safety of zavegepant versus placebo for the acute treatment of migraine in Asian adults. The study intervention is formulated as zavegepant 10 mg IN or matching placebo. The study intervention will be administered using an unidose nasal spray device containing a single dose of zavegepant or matching placebo. The participants will be instructed to take their study intervention, as an outpatient, if they have a migraine headache which reaches moderate or severe pain intensity.

The total duration of study participation will be up to approximately 16 weeks. This includes a 3-28 day Screening Phase, a Treatment Phase that can last up to 45 days or until the participant has a migraine headache that reaches moderate or severe pain intensity, followed by an EOT Visit 7 (+2) days after the administration of study intervention and a Follow-Up Visit 28-35 days after the administration of study intervention for safety monitoring.

Approximately 1750 participants will be screened to randomize approximately 1400 participants in a 1:1 ratio between the 2 treatment groups (zavegepant or placebo). Before any study procedures are performed, participants must sign informed consent. After informed consent is signed, participants will be enrolled in the IRT system. The participant's migraine history and medical history will be collected at the Screening Visit. Participants will also undergo all screening procedures as indicated in the SoA. Screening Visit must be completed in person.

Within 3-28 days from the Screening Visit, participants will return to the site for the Baseline (Randomization) Visit. Participants who meet all eligibility criteria may be randomized at the Baseline Visit. After randomization is completed in the IRT, study intervention will be dispensed to participants to take home for a single attack of moderate or severe pain intensity occurring up to 45 days after the Baseline (Randomization) Visit. The participants will be provided with an eCOA handheld device. The eCOA handheld device may also be referred to as a handheld or an eDiary. Once a participant experiences a migraine headache of moderate to severe intensity, they should record this in the handheld. The handheld will instruct the participant to take study intervention after the initial assessments are completed in the device. The participant will complete assessments for 48 hours after taking study intervention to record efficacy and other quality of life measures. The study personnel **MUST** instruct and train the participant on the proper use of the handheld to **ENSURE** proper understanding and use of the tool, **PRIOR to** the participant leaving the office at Baseline Visit. Baseline Visit must be completed in person. **Participants in this study may be randomized only once. Under NO circumstances may a participant be re-randomized**.

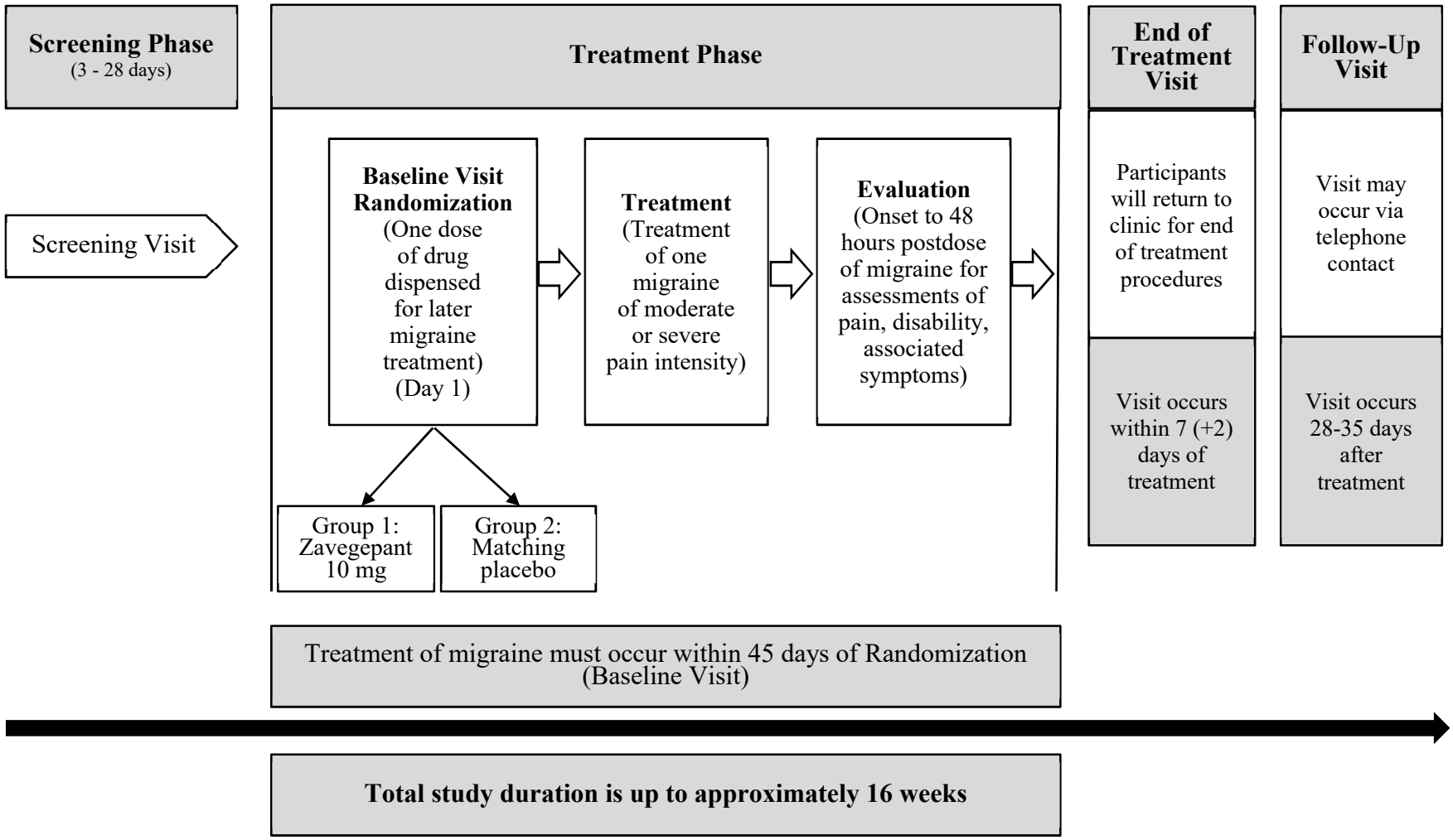
Participants should be encouraged to treat their **FIRST** qualifying migraine attack (moderate or severe pain intensity) that occurs during the Treatment Phase. If participants are unable to treat their first qualifying migraine, refer to Protocol Section 6.9.2. Rescue Medication for a list of medications that are allowed during the course of this study.

Participants will return to the site for EOT Visit (after assessments in the handheld are completed) within 7 (+2) days after administration of study intervention. The "+2" day window is included for scheduling purposes only. Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after administration of study intervention. At the EOT Visit, medication compliance and monitoring of safety assessments will be performed as indicated in the SoA. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete all EOT Visit procedures. All participants must return used and unused study intervention and their handheld device to site. Certain provisions may be implemented, in order to minimize potential hazards to the participants due to COVID-19 **ONLY** at the EOT Visit. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in-home phlebotomy vendors, and shipping of study intervention if needed. Any potential issues should be discussed with sponsor and will be addressed on an individualized basis. Components of the EOT Visit may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.), and the window visit may be

extended by 5 days due to COVID-19 **ONLY** if circumstances warrant in order to minimize any potential risks to participant safety.

Follow-Up Visit will occur 28-35 days after treatment for safety follow-up of AEs and/or abnormal laboratory tests. Participants may be contacted via telephone. Every effort should be made to conduct the Follow-Up Visit within 28-35 days after treatment. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are not required to complete the Follow-Up Visit.

Figure 1. Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The co-primary endpoints are the percentage of participants with a pain intensity of none (pain freedom) at 2 hours postdose, and separately, the percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose.

3.2. Secondary Endpoint(s)

3.2.1. Key Secondary Endpoints

- Percentage of participants with a pain intensity of none or mild (pain relief) at 15 minutes postdose.
- Percentage of participants with a pain intensity of none or mild (pain relief) at 30 minutes postdose.
- Percentage of participants with a pain intensity of none or mild (pain relief) at 2 hours postdose.
- Percentage of participants with a functional disability level of normal at 2 hours postdose, evaluated for participants with functional disability at the time of dosing.
- Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose (sustained pain relief).
- Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose (sustained pain relief).
- Percentage of participants with a functional disability level of normal at 30 minutes postdose, evaluated for participants with functional disability at the time of dosing.
- Percentage of participants with a functional disability level of normal at 60 minutes postdose, evaluated for participants with functional disability at the time of dosing.

3.2.2. Other Secondary Endpoints

- Percentage of participants with phonophobia absent at 2 hours postdose, evaluated for participants with phonophobia present at the time of dosing.
- Percentage of participants with photophobia absent at 2 hours postdose, evaluated for participants with photophobia present at the time of dosing.
- Percentage of participants with nausea absent at 2 hours postdose, evaluated for participants with nausea present at the time of dosing.

- Percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose (sustained pain freedom).

- Percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose (sustained pain freedom).

- Percentage of participants with pain relapse (any pain intensity above 'none') at any time point after 2 hours postdose, evaluated for participant with pain freedom at 2 hours postdose.

- Percentage of participants taking rescue medication within 24 hours postdose.

- Percentage of participants with a pain intensity of none or mild (pain relief) at 60 minutes postdose.

- Percentage of participants with a functional disability level of normal at 15 minutes postdose, evaluated for participants with functional disability at the time of dosing.

- Number and percentage of participants with AEs of moderate or severe intensity, SAEs, local irritation AEs, and grade 3 or 4 laboratory test abnormalities.

3.3. Other Endpoint(s)

The exploratory endpoints include:

- Percentage of participants with a pain intensity of none (pain freedom) at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with an MBS reported before dosing that is absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with a pain intensity of none or mild (pain relief) at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with a functional disability level of normal at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with phonophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with photophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with nausea absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose, respectively.

- Percentage of participants with the overall status improvement at 30 minutes, 60 minutes, 2 hours, and 24 hours postdose, and the total score of PGIC.

3.4. Baseline Variables

The Baseline variables in the study contain demographic and other baseline characteristics as follows.

- Age in years at informed consent (years)
- Age at informed consent category 1: <40, ≥ 40
- Age at informed consent category 2: <65, ≥ 65
- Sex: male, female
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- BMI category: <25 kg/m^2, ≥25 to <30 kg/m^2, ≥ 30 kg/m^2
- Race
- Country/region at randomization
- Stable prophylactic migraine medication use through randomization: yes, no.

3.5. Safety Endpoints

3.5.1. Adverse Events

SAEs and non-serious AEs should be reported from signing of consent through and including a minimum of 28 calendar days after the last administration of the study intervention. The following other significant AEs will be assessed: hepatic-related AEs, potential drug abuse AEs, cardiovascular AEs, suicidality AEs, local irritation AEs, hypertension AEs, and Raynaud's phenomenon AEs.

3.5.2. Laboratory Data

Clinical safety laboratory testing will be performed at Screening, EOT/Early Discontinuation Visits. The baseline value is defined as the last non-missing value on or before the study intervention start date/time.

3.5.3. Vital Signs

The vital signs will be measured at Screening, Baseline, EOT/Early Discontinuation Visits. Vital signs include systolic blood pressure, diastolic blood pressure and pulse rate. The baseline value is defined as the last non-missing value on or before the study intervention start date/time.

3.5.4. 12-lead Electrocardiograms

A 12-lead ECG will be measured at Screening, EOT/Early Discontinuation Visits. ECG parameters include QRS, PR, QT, QTcF, and heart rate. The baseline value is defined as the last non-missing value on or before the study intervention start date/time.

3.5.5. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment. The C-SSRS will be assessed at Screening, Baseline, EOT/Early Discontinuation Visits.

The C-SSRS is made up of ten categories, all of which maintain binary responses (yes/no) to indicate a presence or absence of the suicidal thought or behavior. The C-SSRS findings will be recorded as AEs.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Population	Description	Applicable Analysis (for additional information refer to section 6)
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.	Baseline and other summaries (Section 6.5.2 and Section 6.5.3)

Population	Description	Applicable Analysis (for additional information refer to section 6)
FAS	All participants in the enrolled analysis set who are randomly assigned to study intervention (zavegepant or placebo).	Baseline and other summaries (Section 6.5.2 and 6.5.4)
EAS	All participants in the full analysis set who satisfy the following criteria: • Randomized only once • Have a migraine of moderate or severe pain intensity at the time of dosing • Take study intervention (zavegepant or placebo) • Have postdose efficacy data (ie, non-missing pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level with finding date/time after the study intervention start date/time).	Primary endpoints, secondary endpoints, exploratory endpoints, and baseline summaries (Sections 6.1, 6.2, 6.3, and 6.5.1)
Safety analysis set	All participants in the enrolled analysis set who take study intervention (zavegepant or placebo).	Baseline and other summaries (Section 6.5); Safety summaries and analyses (Section 6.6)

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The treatment comparison being made in this study is zavegepant 10 mg versus placebo. The null and alternative hypotheses are shown below. The test will be 2-sided.

The null hypothesis (H_0) is that the difference in the stratified response rate between treatment groups is zero.

The alternative hypothesis (H_1) is that the difference in the stratified response rate between treatment groups is not zero.

Type I error is controlled by a hierarchical gate-keeping procedure. First, the family of 2 co-primary endpoints is tested. In particular, zavegepant is tested for superiority against placebo at a 2-sided alpha=0.05 level for both co-primary endpoints. If the tests of both co-primary endpoints are significant (ie, both p-values are ≤0.05), then the key secondary endpoints are tested hierarchically at the 2-sided alpha=0.05 level in the order shown in Section 3.2.1. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (ie, p-value ≤0.05). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence will have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For other secondary endpoints and exploratory endpoints, no attempt is made to adjust for multiplicity. Any other secondary endpoints and exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha=0.05 level and presented only for descriptive purposes.

5.2. General Methods

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be summarized using summary statistics (e.g., n, mean, median, standard deviation (SD), minimum, and maximum).

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be summarized as the number and percentage of participants within each category. Percentages in frequency tables are calculated against the number of participants in each treatment group in the specified analysis set. For each endpoint, Mantel-Haenszel risk estimation will be used for the difference in percentages of participants achieving the endpoint response criteria (zavegepant-placebo) stratified by country/region. The difference in percentages between treatment groups will be presented with p-value and asymptotic standard error (ASE) together with a 95% CI based on normal approximation. For individual treatment group, the percentage of participants achieving the endpoint response criteria will be presented with ASE and a 95% CI based on normal approximation.

5.2.3. Time-to-Event Analysis

Time-to-event distribution of endpoints (rescue medication use, pain freedom, MBS freedom, pain relief, normal function, phonophobia absence, photophobia absence, nausea absence) will be tabulated and plotted. Participants are considered to have an event through X hours (X=24 hours or 8 hours) if the first post dose eDiary date/time defining a response is (1) at or before the upper bound of the X-hour analysis window in minutes (see Section 5.2.5), and (2) is before the imputed rescue medication start date/time, if not missing. Otherwise, participants who do not have an event through X hours are censored at the earliest of the following: (1) upper bound of the X-hour analysis window + 1 minute; (2) the imputed first rescue medication start date/time; (3) the last non-missing contact date/time.

For time to rescue medication use through 24 hours, participants are considered to have an event if the date/time of taking the rescue medication is prior to or at 24 hours post dose; otherwise, the time to rescue medication will be considered as censored at the earliest of the following: (1) 24 hours post dose + 1 minute, (2) the last non-missing contact date/time. For time to rescue medication use through 24 hours, the summary table and Kaplan-Meier plot will be using 2-hour time intervals: 0 to <2, >=2 to <4, >=4 to <6, …, >=24. For exploratory endpoints through 8 hours, the summary table and Kaplan-Meier plot will be using the following time intervals: 0 to <15, >=15 to <30, >=30 to <45, >=45 to <60, >=60 to <90, >=90 to <120, >=120 to <180, >=180 to <240, >=240 to <360, >=360 to <495, and >=495 minutes.

The summary table will include the following statistics: number of participants at risk, number of participants with events, number of participants censored for each time interval; overall number and percentage of participants with events and censored; time-to-event estimate for median, first quartile, and third quartile with corresponding 95% CIs. The 95% CI will be estimated using the method of Brookmeyer and Crowley. The log-rank p-value will also be presented for comparison of zavegepant versus placebo.In the Kaplan-Meier plot, the percentage of participants for the endpoints within the time period postdose on the y-axis versus time in minutes on the x-axis will be displayed.

5.2.4. Safety Analysis Periods

Analysis periods	Start date/time	End date/time	Usage
Pre-treatment		Study intervention start date/time	To be used to derive baseline values and to assess the safety endpoints prior to study intervention
On-treatment safety	Study intervention start date/time	Later of (1) Study intervention start date + 9 days and (2) EOT visit date	To be used to assess the safety endpoints during treatment period
Follow-up safety	Later of (1) Study intervention start date + 10 days and (2) EOT visit date + 1 day		To be used to assess the safety endpoints of the follow-up period

5.2.5. Migraine Characteristics and eDiary Analysis Window

The following migraine characteristics are collected on study (i.e., on or after the randomization date) (1) before or at the time of dosing in the eDiary Migraine Report and (2)

postdose from 15 minutes through 48 hours (e.g., 15, 30, 45, 60, and 90 minutes; 2, 3, 4, 6, 8, 24 and 48 hours) in the eDiary Postdose Migraine Report:

- Pain intensity (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia) before dosing in the eDiary Migraine Report only
- Nausea status (present, absent)
- Nausea intensity (mild, moderate, severe), if nausea status is present
- Phonophobia status (present, absent)
- Phonophobia intensity (mild, moderate, severe), if phonophobia status is present
- Photophobia status (present, absent)
- Photophobia intensity (mild, moderate, severe), if photophobia status is present
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura (yes, no) preceding or accompanying headache before dosing in the eDiary Migraine Report only.

The eDiary allows participants to report one result per time point per migraine characteristics parameter.

In general, if participants answered “no” to taking study medication mistakenly already, had current pain intensity of moderate or severe before dosing, and did not use other headache medications, then the eDiary Migraine Report collects current levels of all parameters on study before dosing and at scheduled postdose time points.

Otherwise, if participants answered “yes” to taking study medication mistakenly already and provided the time of study medication taken, then the eDiary Migraine Report collects all parameters listed above (1) retrospectively at the time of dosing except MBS and aura, and (2) prospectively at scheduled postdose time points (as applicable based on study medication time).

For analyses, migraine characteristics collected in the eDiary Migraine Report are considered to be “at the time of dosing”, except MBS and aura, which is considered to be “on study before dosing”.

Windows for postdose efficacy measurements (15, 30, 45, 60, 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours) are automatically assigned by the eDiary as shown in Table 2:

Table 2. eDiary Automated Efficacy Analysis Windows

Postdose Evaluation	Analysis-Specified Interval	Target Time
15 minutes	10 to 20 minutes	Study medication start time + 15 minutes
30 minutes	25 to 35 minutes	Study medication start time + 30 minutes
45 minutes	40 to 50 minutes	Study medication start time + 45 minutes
60 minutes	55 to 65 minutes	Study medication start time + 60 minutes
90 minutes	85 to 95 minutes	Study medication start time + 90 minutes
2 hours	1 hour 55 minutes to 2 hours 15 minutes	Study medication start time + 2 hours
3 hours	2 hour 45 minutes to 3 hours 15 minutes	Study medication start time + 3 hours
4 hours	3 hour 45 minutes to 4 hours 15 minutes	Study medication start time + 4 hours
6 hours	5 hour 45 minutes to 6 hours 15 minutes	Study medication start time + 6 hours
8 Hours	7 hour 45 minutes to 8 hours 15 minutes	Study medication start time + 8 hours
24 hours	23 to 25 hours	Study medication start time + 24 hours
48 hours	47 to 49 hours	Study medication start time + 48 hours

5.3. Methods to Manage Missing Data

Missing data in analyses of binary endpoints are defined as follows:

- Non-Completer=Failure (NC=F): Participants with missing data at a single point are classified as failures. This missing data imputation method is applied to endpoints based on data from a single time point (e.g., co-primary endpoints) as the main analysis method.

- Non-Completer with missing data at more than 1 Time Point=Failure (NC1=F): Participants with missing data at >1 time point postdose in a specified time period are classified as failures. This missing data imputation method is applied to endpoints that are based on data from multiple time points (e.g., secondary endpoints of sustained pain freedom from 2 to 24 hours postdose) as the main analysis method.

In the sensitivity analysis of the co-primary endpoints, the following imputation strategies for missing data will be implemented.

Pain freedom at 2 hours postdose

- Multiple imputation: The main analysis is repeated using the copy from reference multiple imputation approach with m=30 imputations to impute missing pain intensity at 2 hours postdose. The fully conditional specification (FCS) method is used with a generalized logit distribution. Covariates may include country/region at randomization, sex, pain intensity at the time of dosing (moderate or severe), historical number of migraine attacks per month (< median, ≥ median), and MBS before dosing (nausea, phonophobia, or photophobia). First, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed for participants who are not missing any of the covariates (participants missing any of the covariates are considered failures).

- Varying response rate imputation: The main analysis is repeated by imputing missing pain intensity at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure (RM=F, see Appendix 2.1). Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed.

MBS freedom at 2 hours postdose

- Multiple imputation: The main analysis is repeated using the copy from reference multiple imputation approach with m=30 imputations to impute missing MBS status at 2 hours postdose analysis window. First, participants whose MBS before dosing is missing are classified as failures. Next, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure (RM=F). Finally, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed.

- Varying response rate imputation: The main analysis is repeated by imputing missing MBS at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, participants whose MBS before dosing is missing are classified as failures. Next, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure. Finally,

missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The co-primary efficacy endpoints are as follows:

6.1.1. Percentage of participants with a pain intensity of none (pain freedom) at 2 hours postdose

6.1.1.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.1).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

The following statistics are presented:

- Response rate (i.e., "n/N" and percentage), ASE, and 95% CI for each treatment group.
- Stratified percentage difference between treatment groups (zavegepant – placebo), ASE, 95% CI, and p-value.

6.1.1.2. Sensitivity Analyses

- The main analysis is repeated using the copy from reference multiple imputation approach with m=30 imputations to impute missing pain intensity at 2 hours postdose (see Section 5.3).
- The main analysis is repeated by imputing missing data with varying response rates (see Section 5.3).

6.1.2. Percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose

6.1.2.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.1).

- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 hours postdose (RM=F; see Appendix 2.1) and (2) missing MBS at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

The same statistics are tabulated as those for the main analysis of pain freedom at 2 hours postdose (see Section 6.1.1.1).

6.1.2.2. Sensitivity Analysis

- The main analysis is repeated using the copy from reference multiple imputation approach with m=30 imputations to impute missing MBS status at 2 hours postdose (see Section 5.3).
- The main analysis is repeated by imputing missing data with varying response rates (see Section 5.3).

6.2. Secondary Endpoint(s)

6.2.1. Percentage of participants with a pain intensity of none or mild at 15 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 15 minutes postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 15 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relief at 15 minutes postdose (i.e., in the 15-minute postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.2. Percentage of participants with a pain intensity of none or mild at 30 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 30 minutes postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 30 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relief at 30 minutes postdose (i.e., in the 30-minute postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.3. Percentage of participants with a pain intensity of none or mild at 2 hours postdose

- Estimand strategy: Composite policy (Section 2.2.2).

- Analysis set: EAS (Section 4).

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relief at 2 hours postdose (i.e., in the 2-hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.4. Return to normal function at 2 hours postdose

Return to normal function at a single time point postdose is defined as a functional disability level of normal at that time point for participants with functional disability at the time of dosing.

- Estimand strategy: Composite policy (Section 2.2.2).

- Analysis set: EAS (Section 4). Participants with functional disability at the time of dosing will be included.

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 hours postdose (RM=F; see Appendix 2.1) and (2) missing functional disability level at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with return to normal function at 2 hours postdose (i.e., in the 2-hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.5. Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 24 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2 or 24 hours postdose (NC=F; see Section 5.3 for definition) and (3) missing pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with sustained pain relief from 2 to 24 hours (i.e., in the 2 to 24 hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.6. Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 48 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2, 24 or 48 hours postdose (NC=F; see Section 5.3 for definition) and (3) missing pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with sustained pain relief from 2 to 48 hours (i.e., in the 2 to 48 hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.7. Return to normal function at 30 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4). Participants with functional disability at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 30 minutes postdose (RM=F; see Appendix 2.1) and (2) missing functional disability level at 30 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with return to normal function at 30 minutes postdose (i.e., in the 30-minute postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.8. Return to normal function at 60 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4). Participants with functional disability at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 60 minutes postdose (RM=F; see Appendix 2.1) and (2) missing functional disability level at 60 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with return to normal function at 60 minutes postdose (i.e., in the 60-minute postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.9. Freedom from phonophobia at 2 hours postdose

Freedom from phonophobia at a single time point postdose is defined as phonophobia absent at that time point for participants with the phonophobia present at the time of dosing.

- Estimand strategy: Composite policy (Section 2.2.2).

- Analysis set: EAS (Section 4). Participants with phonophobia present at the time of dosing will be included.

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 horus postdose (RM=F; see Appendix 2.1) and (2) missing phonophobia status at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with phonophobia freedom at 2 hours postdose (i.e., in the 2-hour postdose analysis window) present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.10. Freedom from photophobia at 2 hours postdose

Freedom from photophobia at a single time point postdose is defined as photophobia absent at that time point for participants with the photophobia present at the time of dosing.

- Estimand strategy: Composite policy (Section 2.2.2).

- Analysis set: EAS (Section 4). Participants with photophobia present at the time of dosing will be included.

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 horus postdose (RM=F; see Appendix 2.1) and (2) missing photophobia status at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with photophobia freedom at 2 hours postdose (i.e., in the 2-hour postdose analysis window) present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.11. Freedom from nausea at 2 hours postdose

Freedom from nausea at a single time point postdose is defined as nausea absent at that time point for participants with the nausea present at the time of dosing.

- Estimand strategy: Composite policy (Section 2.2.2).

- Analysis set: EAS (Section 4). Participants with nausea present at the time of dosing will be included.

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 2 horus postdose (RM=F; see Appendix 2.1) and (2) missing nausea status at 2 hours postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with nausea freedom at 2 hours postdose (i.e., in the 2-hour postdose analysis window) present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.12. Percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 24 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2 or 24 hours postdose (NC=F; see Section 5.3 for definition) and (3) missing pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with sustained pain freedom from 2 to 24 hours (i.e., in the 2 to 24 hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.13. Percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 48 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 2, 24 or 48 hours postdose (NC=F; see Section 5.3 for definition) and (3) missing pain intensity at >1 time point from 3 to 8 hours postdose (NC1=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with sustained pain freedom from 2 to 48 hours (i.e., in the 2 to 48 hour postdose analysis window) will present similar

statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.14. Percentage of participants with pain relapse at any time point after 2 hours postdose

Pain relapse at any time point after 2 hours postdose is defined as pain intensity of mild, moderate, or severe at any time point after 2 hours postdose for participants with pain intensity of none at 2 hours postdose.

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4). Participants with pain freedom at 2 hours postdose will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 48 hours postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at >1 time point from 3 to 48 hours postdose (NC1=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relapse at any time point after 2 hours postdose (i.e., in the 3 to 48 hour postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.15. Percentage of participants taking rescue medication within 24 hours postdose

6.2.15.1. Main Analysis

- Estimand strategy: Not applicable (Section 2.2.2).
- Analysis set: EAS (Section 4). Participants in the EAS with first rescue medication date ≤ study intervention start date + 1 day and missing first rescue medication time are excluded.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2. In addition, rescue medications will be tabulated by therapeutic class and preferred name.
- Intercurrent events and missing data: No relevant intercurrent is considered since taking rescue mediation is the analysis objective.

Treatment group comparisons of the percentage of participants using rescue medication within 24 hours postdose will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

Rescue medications are concomitant medications that meet all the following criteria:

- "Rescue Medications" response to the question "Category" from the Concomitant Medications-Rescue Medicine CRF
- Taking rescue medication within 24 hours post dose is defined as rescue medication use ≤ 24 hours. No analysis window around the 24-hour postdose timepoint is used.

6.2.15.2. Supportive Analysis

Time to rescue medication use through 24 hours postdose is assessed by treatment group using the approach as described in Section 5.2.3. Rescue medication use through 24-hours postdose is considered as an event.

6.2.16. Percentage of participants with a pain intensity of none or mild at 60 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before 60 minutes postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at 60 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relief at 60 minutes postdose (i.e., in the 60-minute analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.2.17. Return to normal function at 15 minutes postdose

- Estimand strategy: Composite policy (Section 2.2.2).
- Analysis set: EAS (Section 4). Participants with functional disability at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before 15 minutes postdose (RM=F; see Appendix 2.1) and (2) missing functional disability level at 15 minutes postdose (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with return to normal function at 15 minutes postdose (i.e., in the 15-minute postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3. Exploratory Endpoints

6.3.1. Percentage of participants with a pain intensity of none at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.1.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3)
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the assessed time points postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at each of the assessed time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain freedom at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.1.2. Supportive Analysis

Time to pain freedom through 8 hours postdose distribution will be presented, separately. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.2. Percentage of participants with an MBS reported before dosing that is absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.2.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).

- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing MBS status at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with MBS at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.2.2. Supportive Analysis

Time to MBS freedom through 8 hours postdose distribution will be presented. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.3. Percentage of participants with a pain intensity of none or mild (pain relief) at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.3.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).
- Analysis set: EAS (Section 4).
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing pain intensity at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with pain relief at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.3.2. Supportive Analysis

Time to pain relief through 8 hours postdose distribution will be presented, separately. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.4. Percentage of participants with a functional disability level of normal at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.4.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).
- Analysis set: EAS (Section 4). Participants with functional disability at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing functional disability level at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with return to normal function at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.4.2. Supportive Analysis

Time to return to normal function through 8 hours postdose distribution will be presented, separately. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.5. Percentage of participants with phonophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.5.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).
- Analysis set: EAS (Section 4). Participants with phonophobia present at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing phonophobia status at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with phonophobia freedom at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.5.2. Supportive Analysis

Time to phonophobia freedom through 8 hours postdose distribution will be presented. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.6. Percentage of participants with photophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.6.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).
- Analysis set: EAS (Section 4). Participants with photophobia present at the time of dosing will be included.
- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.
- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing photophobia status at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with photophobia freedom at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.6.2. Supportive Analysis

Time to photophobia freedom through 8 hours postdose distribution will be presented. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.7. Percentage of participants with nausea absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours, and 48 hours postdose

6.3.7.1. Main Analysis

- Estimand strategy: Composite policy (Section 2.2.3).

- Analysis set: EAS (Section 4). Participants with nausea present at the time of dosing will be included.

- Analysis methodology: The Mantel-Haenszel risk estimation stratified by country/region will be used. See details in Section 5.2.2.

- Intercurrent events and missing data: (1) Taking rescue medication at or before each of the time points postdose (RM=F; see Appendix 2.1) and (2) missing nausea status at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

Treatment group comparisons of the percentage of participants with nausea freedom at each time point from 15 minutes through 48 hours postdose (i.e., in the 15-minute to 48 hours postdose analysis window) will present similar statistics as the main analysis of the co-primary endpoint of pain freedom (see Section 6.1.1.1).

6.3.7.2. Supportive Analysis

Time to nausea freedom through 8 hours postdose distribution will be presented. Kaplan-Meier plot will also be displayed (see Section 5.2.3 for details).

6.3.8. Percentage of participants with the PGIC overall status improvement at 30 minutes, 60 minutes, 2 hours, and 24 hours postdose

The overall status based on PGIC total score will be categorized into 3 categories: (1) improved (defined as very much improved, much improved, or minimally improved); (2) worse (defined as minimally worse, much worse, or very much worse); (3) no change

At each time point postdose, number and percentage of participants in above 3 categories will be tabulated by treatment group.

For the percentage of participants with the PGIC overall status improvement (above category 1), the ASE and a 95% CI based on normal approximation will be presented for each group and the Mantel-Haenszel risk estimation stratified by country/region will be used for percentage difference between treatment groups with ASE, 95% CI, and p-value presented (See Section 5.2.2). Taking rescue medication at or before each of the time points postdose will be regarded as failures (RM=F; see Appendix 2.1) and the missing PGIC overall status at each of the time points postdose respectively (NC=F; see Section 5.3 for definition) will be regarded as failures.

6.4. Subset Analyses

For the co-primary and key secondary endpoints, subgroup analyses will be conducted for the following baseline demographic and characteristic variables:

- Country/region at randomization: China, Korea, Taiwan
- Age at informed consent category 1: <40, ≥ 40

- Sex: male, female
- BMI category: <25 kg/m^2, ≥25 to <30 kg/m^2, ≥ 30 kg/m^2
- Aura on study before dosing: yes, no
- History of migraine with aura: yes, no (see Section 6.5.1.2)
- Historical number of moderate to severe migraine attacks per month: <4, ≥4 (overall median)
- Stable prophylactic migraine medication use through randomization: yes, no.

For the primary endpoint of "percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose", the following characteristic variables will additionally be used for subgroup analysis:

- MBS on study before dosing: Nausea
- MBS on study before dosing: Phonophobia
- MBS on study before dosing: Photophobia

Main analysis method descripted in Section 5.2.2 will be used, except for the subgroup analysis by country/region at randomization, in which Mantel-Haenszel risk estimation without stratification will be conducted.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline summaries will include the following: demographics and other relevant baseline characteristics, migraine history, migraine characteristic at the time of dosing, medical history, and prior non-study medications. Unless specified otherwise, baseline summaries will be presented for EAS and safety analysis set, respectively.

6.5.1.1. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the variables listed in Section 3.4.

6.5.1.2. Migraine History

Migraine history will include the following:

- Age (years) at migraine onset
- Time since last migraine (days)
- Number of moderate to severe migraines per month, also categorized as < median, ≥ median, where the median is calculated overall across treatment groups combined for the efficacy analysis set and rounded to an integer
- Average duration of untreated migraine attacks (hours)

- Most bothersome symptom (i.e., nausea and/or vomitting, photophobia, or phonophobia)
- Migraine symptoms (i.e., headache attacks lasting 4-72 hours, unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, nausea and/or vomiting during headache, photophobia and phonophobia during headache)
- History of migraine without aura (yes, no)
- History of migraine with aura (yes, no)

6.5.1.3. Migraine Characteristics at the Time of Dosing

Migraine characteristics at the time of dosing include the following parameters:

- Pain intensity (none, mild, moderate, severe)
- MBS (nausea, phonophobia, photophobia) on study before dosing
- Nausea status (present, absent)
- Nausea intensity (none, mild, moderate, severe)
- Phonophobia status (present, absent)
- Phonophobia intensity (none, mild, moderate, severe)
- Photophobia status (present, absent)
- Photophobia intensity (none, mild, moderate, severe)
- Functional disability level (normal, mildly impaired, severely impaired, requires bedrest)
- Aura (yes, no) on-study before dosing.

An intensity of none for a symptom (nausea, photophobia, or phonophobia) is defined as a symptom status of absent. See Section 5.2.5 for additional details.

6.5.1.4. Medical History

Medical history will be summarized by system organ class (SOC) and preferred term (PT), and displayed in descending order of overall frequency within SOC and PT.

A separate table summarizing the medical history of hypertension will be produced. A participant is considered to have medical history of hypertension if ≥1 medical history PTs are among the prespecified list of PTs defined in Section 6.6.1.3.

6.5.1.5. Non-study Medications

The following non-study medications are tabulated by preferred name using safety analysis set:

- Prior medications: defined as those taken before study intervention starts.
- Concomitant medications: defined as those taken on or after study intervention starts. Non-study concomitant rescue medications will be additionally tabulated in a separate summary.
- Stable prophylactic migraine medications through randomization: defined as prophylactic migraine medication taken > 3 months before informed consent and through randomization.

6.5.2. Participant Disposition

Participant disposition will be summarized for all randomized participants (FAS) by study phase including the number and percentages of participants enrolled, treated, completed the study, discontinued from the study and the primary reason of discontinuation.

6.5.3. Summary of Analysis Sets

The number and percentage of participants screened and included in each analysis set as defined in Section 4 will be summarized.

6.5.4. Study Treatment Exposure

Study intervention exposure is summarized by treatment group for FAS that includes the number and percentage of participants in the following categories:

- Study intervention taken (i.e., study intervention start date/time not missing)
  - Study intervention actually received different from randomized treatment assignment
- Study intervention not taken (i.e., study intervention start date/time missing)

6.6. Safety Summaries and Analyses

Safety analyses are based on the safety analysis set by as-treated treatment group. Safety parameters include death, AEs, laboratory tests, vital signs, and ECGs.

6.6.1. Adverse Events

6.6.1.1. AE Overview

An AE overview without SOC and PT will present the number of participants evaluable for adverse events, the number of adverse events, the number and percentage of participants with: any AE; mild AE; moderate AE; severe AE; moderate or severe AE; SAE; AE leading to study discontinuation; hepatic-related AE; potential drug abuse AE; cardiovascular AE; suicidality AE; local irritation AE; hypertension AE; Raynaud's phenomenon AE.

An AE overview will be produced by treatment group for each analysis period as defined in Section 5.2.4 using the safety analysis set. All-cause TEAEs (for on-treatment period and follow-up period) and treatment-related TEAEs (for on-treatment period) will be generated separately.

6.6.1.2. AEs by SOC and PT

All-cause TEAEs (for each analysis period) and treatment-related TEAEs (for on-treatment period) will be generated separately for below summaries.

6.6.1.2.1. Pre-treatment AEs

Pre-treatment AEs will not be summarized, and will be included in the AE listing.

6.6.1.2.2. On-Treatment Treatment Emergent AEs (TEAE)

An AE is considered a treatment-emergent AE if the event started after the study intervention start date/time. All-cause and treatment-related TEAEs will be summarized by SOC and PT for the safety analysis set by treatment group for the following endpoints:

- TEAEs
- TEAEs by severity (total, mild, moderate, severe, not reported)
- SAEs

6.6.1.2.3. Follow-up TEAEs

Follow-up TEAEs will be summarized by SOC and PT for safety analysis set by treatment group for the following:

- TEAEs
- TEAEs by severity (total, mild, moderate, severe, not reported)
- SAEs.

6.6.1.3. Other Significant AEs

All-cause (for on-treatment period and follow-up period) and treatment-related (for on-treatment period) AEs will be generated separately for other significant AEs, which will be summarized by SOC and PT for the safety analysis set by treatment group:

- Hepatic-related AEs
- Cardiovascular AEs
- Suicidality AEs
- Local irritation AEs
- Potential drug abuse AEs
- Hypertension AEs
- Raynaud's phenomenon AEs

Potential drug abuse AEs will be displayed in alphabetical order by severity and PT without SOC.

Definitions of the above AEs are described in the following and Appendix 3.1, and are subject to change due to sponsor internal update; minor updates to the definitions will be included in the programming A&R plan before study database lock.

Hepatic-Related AEs

Hepatic-related AE PTs will include the following:

- "Hepatic disorders" SMQ: All PTs except those in "Congenital, familial, neonatal and genetic disorders of the liver" SMQ.

Potential Drug Abuse AEs

Potential drug abuse AE PTs will include any of the following:

- "Drug abuse, dependence and withdrawal" SMQ: All PTs
- PTs in Table 3 (Appendix 3.1). This list is based on clinical review of AE PTs in the depressant, stimulant, and psychotomimetic categories of the General disorders and administration site conditions SOC, Nervous system disorders SOC, and Psychiatric disorders SOC, as recommended in FDA Guidance for Industry Assessment of Abuse Potential of Drugs Section V.B (January 2017). Note that some PTs in this list are also part of the "Drug abuse, dependence and withdrawal" SMQ.

- PT of dizziness only if concurrent with any euphoria-related AE in Table 4 (Appendix 3.1), which is a subset of PTs in Table 3 (Appendix 3.1).
    - For a given safety analysis period, AEs are considered concurrent if (1) their durations overlap, and (2) their AE start dates are in the same safety analysis period.

Cardiovascular AEs

Cardiovascular AE PTs include the following:

- "Conditions associated with central nervous system haemorrhages and cerebrovascular Accidents" SMQ: Narrow PTs
- "Ischaemic central nervous system vascular conditions" SMQ: Narrow PTs
- "Embolic and thrombotic events, arterial" SMQ: peripheral arterial occlusive disease; peripheral arterial reocclusion; peripheral artery angioplasty; peripheral artery bypass; peripheral artery occlusion; peripheral artery stent insertion; peripheral artery thrombosis
- "Ischaemic colitis" SMQ: Narrow PTs
- "Ischaemic heart disease" SMQ
    - "Myocardial infarction" SMQ: Narrow PTs
    - "Other ischaemic heart disease" SMQ: Narrow PTs

Suicidality AEs

Suicidality AE PTs include the following:

- "Suicide/self-injury" SMQ: All PTs.

Local Irritation AEs

Local irritation AE PTs include any of the following:

- "Administrative site reactions NEC" high level term (HLT): PTs in Table 5 (Appendix 3.2) based on clinical review. NEC=not elsewhere classified.
- "Upper respiratory tract signs and symptoms" HLT: PTs in Table 6 (Appendix 3.2) based on clinical review.
- Dysgeusia.

Hypertension AEs

Hypertension AE PTs include the following:

- "Hypertension" SMQ: Narrow PTs

These AEs will also be summarized for the subgroup of participants with medical history of hypertension.

Raynaud's Phenomenon AEs

- AEs with the PT of Raynaud's phenomenon are included.

6.6.1.4. TEAEs Leading to Discontinuation of Study

All-cause and treatment-related TEAEs leading to discontinuation of study will be summarized by treatment group.

6.6.2. Laboratory Data

Laboratory test results will be graded according to numeric laboratory test criteria in Common Terminology Criteria for Adverse Events (CTCAE) if available; otherwise according to Division of Acquired Immune Deficiency Syndrome (DAIDS) Table for Grading the Intensity of Adult and Pediatric Adverse Events. See (Appendix 4) for details about toxicity grading. Laboratory test groups of clinical interest will include hematology, chemistry, and urinalysis.

Values and changes from baseline in laboratory tests are tabulated as continuous variables at Baseline and EOT for the treatment analysis period by treatment group for the safety analysis set.

Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI equations as defined in Appendix 10.6 of study protocol v1.0 and the lower limit of normal (LLN) is set to 90 mL/min/1.73m^2.

6.6.2.1. Laboratory Test Abnormalities

Laboratory test abnormalities are summarized as the number and percentages of participants in the safety analysis set in the following frequency tables:

- Worst (highest) on-treatment laboratory test abnormality for each graded laboratory test.

6.6.2.2. Liver Function Test (LFT) Elevations

LFT Elevations: Cumulative, Mutually Exclusive, and Composite

The number and percentage of participants with LFT elevations will be summarized for the safety analysis set for pre-treatment period and on-treatment analysis periods, respectively. LFT elevations are based on fold changes above ULN.

LFT elevations include the following categories:

- Cumulative elevations:
  - ALT > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - ALT or AST > 1 x, > 3 x, > 5 x, > 10 x, and > 20 x ULN
  - TBL > 1 x, > 1.5 x, and > 2 x ULN
  - ALP > 1 x, > 1.5 x, and > 2 x ULN
- Mutually exclusive elevations:
  - ALT > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - ALT or AST > ULN to ≤ 3 x ULN, > 3 x ULN to ≤ 5 x ULN, > 5 x ULN to ≤ 10 x ULN, > 10 x ULN to ≤ 20 x ULN, and > 20 x ULN
  - TBL > ULN to ≤1.5 x ULN, > 1.5 x ULN to ≤ 2 x ULN, and > 2 x ULN
  - ALP > ULN to ≤ 1.5 x ULN, > 1.5 x ULN to ≤ 2 x ULN, and > 2 x ULN
- Composite elevations:
  - ALT or AST > 3 x ULN and TBL > 1.5 x ULN
  - ALT or AST > 3 x ULN and TBL > 2 x ULN
  - ALT or AST > 3 x ULN concurrent with TBL > 2 x ULN. Concurrent is defined as elevations on the same collection date.
  - ALT or AST > 3 x ULN concurrent with TBL > 2 x ULN and ALP ≤ 2 x ULN. Concurrent is defined as elevations on the same collection date.

- ALT or AST > 3 x ULN concurrent with a selected AE:
  - The following PTs are used to identify selected AEs: nausea, vomiting, decreased appetite, fatigue, and those containing "abdominal pain".
  - Results are also displayed for each selected AE
  - For a given safety analysis period, an LFT elevation is concurrent with an AE of interest if the imputed AE start date is +/- 7 days inclusive of the LFT collection date; both the LFT collection date and the imputed AE start date must also be in the safety analysis period.

eDISH Scatter Plot

An evaluation of drug-induced serious hepatotoxicity (eDISH) scatter plot on-treatment period displays the maximum TBL ratio of value to ULN on the y-axis versus the maximum ALT ratio of value to ULN on the x-axis, where the maxima are in the on-treatment safety analysis period but not necessarily concurrent. Both axes are on the log10 scale with minima of 0.1. Ratios < 0.1x ULN are set to 0.1. Sample sizes in the legend redisplay participants with paired ratios during the on-treatment safety analysis period. A horizontal reference line is placed at 2x ULN, and a vertical reference line is placed at 3x ULN. The lower left quadrant is labeled "Normal Range", the upper left quadrant is labeled "Hyperbilirubinemia", the lower right quadrant is labeled "Temple's Corollary", and the upper right quadrant is labeled "Possible Hy's Law Range." A footnote specifies that "Ratios < 0.1x ULN are set to 0.1", and is displayed only if ≥ 1 participant has a ratio set to 0.1.

6.6.3. Vital Signs

Values and changes from baseline in vital signs will be summarized as continuous variables at Baseline and EOT of the on-treatment safety analysis period by treatment group for the safety analysis set. A separate table of values and changes from baseline in vital signs will be generated for the subgroup of participants with medical history of hypertension.

Vital sign abnormalities during on-treatment period will be summarized by treatment group as the number and percentage of participants in the following categories:

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Pulse rate (bpm)	min. <40	max. >120

A separate table of vital sign abnormalities during on-treatment period for the subgroup of participants with medical history of hypertension will be generated using the following abnormality categories:

Systolic BP (mm Hg)	min. <90	max. >140 max. >160
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	max. >90 max. >100
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Pulse rate (bpm)	min. <40 min. <60	max. >100 max. >120

6.6.4. Electrocardiograms

Values and changes from baseline in ECG parameters will be summarized as continuous variables by treatment group at Baseline and EOT of the on-treatment safety analysis period for the safety analysis set. Results for overall are only shown at Baseline.

ECG abnormalities during on-treatment period will be summarized by treatment group as the number and percentage of participants in the following categories:

- QTcF (msec): > 450 to 480, > 480 to 500, > 500.
- QTcF interval increase from baseline (msec): > 30 to 60, >60.

6.6.5. Columbia Suicide Severity Rating Scale (C-SSRS)

Frequency table by treatment group will be provided for C-SSRS suicidality on-treatment period in the safety analysis set.

7. INTERIM ANALYSES

7.1. Introduction

No interim analysis will be conducted for this study.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Percentage of participants with pain freedom at 2 hours postdose	Main analysis for the co-primary endpoints	EAS	Taking rescue medication at or before 2 hours postdose or missing pain intensity at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Sensitivity analysis	EAS	Taking rescue medication at or before 2 hours postdose will be regarded as a failure. Missing data will be imputed.	Copy from reference multiple imputation approach
	Sensitivity analysis	EAS	Taking rescue medication at or before 2 hours postdose will be regarded as a failure. Missing data will be imputed.	Varying response rates for imputation
Percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose	Main analysis for the co-primary endpoints	EAS	Taking rescue medication at or before 2 hours postdose or missing MBS status at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Sensitivity analysis	EAS	Taking rescue medication at or before 2 hours postdose will be	Copy from reference multiple

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
			regarded as a failure. Missing data will be imputed.	imputation approach
	Sensitivity analysis	EAS	Taking rescue medication at or before 2 hours postdose will be regarded as a failure. Missing data will be imputed.	Varying response rates for imputation
Percentage of participants with a pain intensity of none or mild at 15 minutes postdose	Secondary analysis	EAS	Taking rescue medication at or before 15 minutes postdose or missing pain intensity at 15 minutes postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with a pain intensity of none or mild at 30 minutes postdose	Secondary analysis	EAS	Taking rescue medication at or before 30 minutes postdose or missing pain intensity at 30 minutes postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with a pain intensity of none or mild at 2 hours postdose	Secondary analysis	EAS	Taking rescue medication at or before 2 hours postdose or missing pain intensity at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Return to normal function at 2 hours postdose	Secondary analysis	EAS with functional disability at	Taking rescue medication at or before 2 hours postdose or missing functional disability level at 2 hours	Mantel-Haenszel risk estimation stratified by

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
		time of dosing	postdose will be regarded as failures.	country/region at randomization
Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose	Secondary analysis	EAS	(1) Taking rescue medication at or before 24 hours postdose, (2) missing pain intensity at 2 or 24 hours postdose, or (3) missing pain intensity at > 1 time point from 3 to 8 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose	Secondary analysis	EAS	(1) Taking rescue medication at or before 48 hours postdose, (2) missing pain intensity at 2, 24 or 48 hours postdose, or (3) missing pain intensity at > 1 time point from 3 to 8 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Return to normal function at 30 minutes postdose	Secondary analysis	EAS with functional disability at time of dosing	Taking rescue medication at or before 30 minutes postdose or missing functional disability level at 30 minutes postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Return to normal function at 60 minutes postdose	Secondary analysis	EAS with functional disability at	Taking rescue medication at or before 60 minutes postdose or missing functional disability level at	Mantel-Haenszel risk estimation stratified by

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
		time of dosing	60 minutes postdose will be regarded as failures.	country/region at randomization
Freedom from phonophobia at 2 hours postdose	Secondary analysis	EAS with phonophobia present at time of dosing	Taking rescue medication at or before 2 hours postdose or missing phonophobia status at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Freedom from photophobia at 2 hours postdose	Secondary analysis	EAS with photophobia present at time of dosing	Taking rescue medication at or before 2 hours postdose or missing photophobia status at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Freedom from nausea at 2 hours postdose	Secondary analysis	EAS with nausea present at time of dosing	Taking rescue medication at or before 2 hours postdose or missing nausea status at 2 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with pain freedom at all time points from 2 to 24 hours postdose	Secondary analysis	EAS	(1) Taking rescue medication at or before 24 hours postdose, (2) missing pain intensity at 2 or 24 hours postdose, or (3) missing pain intensity at > 1 time point from 3 to 8 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Percentage of participants with pain freedom at all time points from 2 to 48 hours postdose	Secondary analysis	EAS	(1) Taking rescue medication at or before 48 hours postdose, (2) missing pain intensity at 2, 24 or 48 hours postdose, or (3) missing pain intensity at > 1 time point from 3 to 8 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with pain relapse at any time point after 2 hours postdose	Secondary analysis	EAS with pain freedom at 2 hours postdose	Taking rescue medication at or before 48 hours postdose or missing pain intensity at >1 time point from 3 to 48 hours postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants taking rescue medication within 24 hours postdose	Secondary analysis	EAS	Observed data	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS	Observed data	Time-to-event
Percentage of participants with a pain intensity of none or mild at 60 minutes postdose	Secondary analysis	EAS	Taking rescue medication at or before 60 minutes postdose or missing pain intensity at 60 minutes postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Return to normal function at 15 minutes postdose	Secondary analysis	EAS	Taking rescue medication at or before 15 minutes postdose or missing functional disability level at 15 minutes postdose will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
Percentage of participants with pain freedom at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS	Taking rescue medication at or before each of the assessed time points postdose or missing pain intensity at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS	Observed data	Time-to-event Kaplan-Meier
Percentage of participants with an MBS reported before dosing that is absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS	Taking rescue medication at or before each of the assessed time points postdose or missing MBS status at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS with MBS reported on	Observed data	Time-to-event Kaplan-Meier

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
		study before dosing		
Percentage of participants with a pain intensity of none or mild at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS	Taking rescue medication at or before each of the assessed time points postdose or missing pain intensity at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS	Observed data	Time-to-event Kaplan-Meier
Percentage of participants with a functional disability level of normal at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS with functional disability at the time of dosing	Taking rescue medication at or before each of the assessed time points postdose or missing functional disability level at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS with functional disability at	Observed data	Time-to-event Kaplan-Meier

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
		the time of dosing		
Percentage of participants with phonophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS with phonophobia present at the time of dosing	Taking rescue medication at or before each of the assessed time points postdose or missing phonophobia status at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS with phonophobia present at the time of dosing	Observed data	Time-to-event Kaplan-Meier
Percentage of participants with photophobia absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS with photophobia present at the time of dosing	Taking rescue medication at or before each of the assessed time points postdose or missing photophobia status at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS with photophobia present at	Observed data	Time-to-event Kaplan-Meier

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
		the time of dosing		
Percentage of participants with nausea absent at 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 24 hours and 48 hours	Exploratory analysis	EAS with nausea present at the time of dosing	Taking rescue medication at or before each of the assessed time points postdose or missing nausea status at each of the assessed time points postdose respectively will be regarded as failures.	Mantel-Haenszel risk estimation stratified by country/region at randomization
	Supportive analysis	EAS with nausea present at the time of dosing	Observed data	Time-to-event Kaplan-Meier
Percentage of participants with the PGIC overall status improvement at 30 minutes, 60 minutes, 2 hours, and 24 hours postdose	Summary	EAS	Observed data	Mantel-Haenszel risk estimation stratified by country/region at randomization

Appendix 2. Data Derivation Details

Appendix 2.1. Endpoint Derivations

Appendix 2.1.1. Efficacy Endpoint Derivations

Let X denote a planned time point postdose: 15, 30, 45, 60, or 90 minutes; 2, 3, 4, 6, 8, 24, or 48 hours.

Pain Freedom over Time

At time point X, participants who meet both of the following criteria are classified as responders:

- Pain intensity of none at X, i.e., in the X analysis window
- No rescue medication taken at or before the pain intensity assessment in the X analysis window.

At time point X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F)
- Mild, moderate, or severe pain intensity at X
- Missing pain intensity at X (NC=F).

MBS Freedom over Time

At time point X, participants who meet both of the following criteria are classified as responders:

- MBS reported before dosing that is absent at X, i.e., in the X analysis window
- No rescue medication taken at or before the MBS status assessment in the X analysis window.

At time point X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Missing MBS before dosing
- Rescue medication taken at or before X (RM=F)
- MBS present at X, e.g., nausea reported as MBS before dosing and nausea status of present in the X analysis window
- Missing MBS at X (NC=F), e.g., nausea reported as MBS before dosing and missing nausea status in the X analysis window.

Pain Relief over Time

At time point X, participants who meet both of the following criteria are classified as responders:

- Pain intensity of none or mild at X, i.e., in the X analysis window
- No rescue medication taken at or before the pain intensity assessment in the X analysis window.

At time point X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F)
- Moderate or severe pain intensity at X
- Missing pain intensity at X (NC=F).

Return to Normal Function over Time

This endpoint is evaluated in the subset of participants with functional disability at the time of dosing.

At time point X, participants who meet both of the following criteria are classified as responders:

- Functional disability level of normal at X, i.e., in the X analysis window
- No rescue medication taken at or before the functional disability level assessment in the X analysis window.

At time point X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F)
- Functional disability level of mildly impaired, severely impaired, or requires bedrest at X
- Missing functional disability level at X (NC=F).

Freedom from Photophobia, Phonophobia, or Nausea over Time

Symptom freedom at a single time point postdose is defined as a symptom status of absent at that time point for the subset of participants with symptom status of present at the time of dosing.

For symptom freedom at X, participants who meet both of the following criteria are classified as responders:

- Symptom status of absent at X, i.e., in the X analysis window

- No rescue medication taken at or before the symptom status assessment in the X analysis window

For symptom freedom at X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F)
- Symptom status of present at X
- Missing symptom status at X (NC=F).

Sustained Pain Relief at 2 to 24 Hours Postdose

Sustained pain relief from 2 to 24 hours postdose is defined as pain intensity of none or mild at all time points from 2 to 24 hours postdose.

Participants who meet all the following criteria are classified as responders:

- Pain intensity of none or mild at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before the pain intensity assessment in the 24-hour postdose analysis window.

Participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken 24 hours postdose (RM=F)
- Moderate or severe pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8, or 24-hour postdose analysis window
- Missing pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Sustained Pain Relief from 2 to 48 Hours Postdose

Sustained pain relief from 2 to 48 hours postdose is defined as pain intensity of none or mild at all time points from 2 to 48 hours postdose.

Participants who meet all the following criteria are classified as responders:

- Pain intensity of none or mild at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows

- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before the pain intensity assessment in the 48-hour postdose analysis window.

Participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F)
- Moderate or severe pain intensity at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Sustained Pain Freedom from 2 to 24 Hours Postdose

Sustained pain freedom from 2 to 24 hours postdose is defined as pain intensity of none at all time points from 2 to 24 hours postdose.

Participants who meet all the following criteria are classified as responders:

- Pain intensity of none at all time points from 2 to 24 hours postdose, i.e., in the 2 to 24-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before the pain intensity assessment in the 24-hour postdose analysis window.

Participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 24 hours postdose (RM=F)
- Mild, moderate, or severe pain intensity at any time point from 2 to 24 hours postdose, i.e., in the 2, 3, 4, 6, 8, or 24-hour postdose analysis window
- Missing pain intensity at 2 or 24 hours postdose (NC=F), i.e., in the 2 or 24-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Sustained Pain Freedom from 2 to 48 Hours Postdose

Sustained pain freedom from 2 to 48 hours postdose is defined as pain intensity of none at all time points from 2 to 48 hours postdose.

Participants who meet all the following criteria are classified as responders:

- Pain intensity of none at all time points from 2 to 48 hours postdose, i.e., in the 2 to 48-hour postdose analysis windows
- Missing pain intensity at ≤ 1 time point from 3 to 8 hours postdose, i.e., in the 3, 4, 6, or 8-hour postdose analysis windows
- No rescue medication taken at or before the pain intensity assessment in the 48-hour postdose analysis window.

Participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F)
- Mild, moderate, or severe pain intensity at any time point from 2 to 48 hours postdose, i.e., in the 2, 3, 4, 6, 8, 24, or 48-hour postdose analysis window
- Missing pain intensity at 2, 24, or 48 hours postdose (NC=F), i.e., in the 2, 24, or 48-hour postdose analysis window
- Missing pain intensity at > 1 time point from 3 to 8 hours postdose (NC1=F), i.e., in the 3, 4, 6, or 8-hour postdose analysis window.

Pain Relapse from 2 to 48 Hours Postdose

Pain relapse from 2 to 48 hours postdose is defined as pain intensity of mild, moderate, or severe at any time point after 2 hours postdose for the subset of participants with pain freedom (i.e., pain intensity of none) at 2 hours postdose.

Participants who meet all the following criteria are classified as non-relapsers:

- Pain intensity of none at all time points after 2 hours postdose, i.e., in the 3 to 48-hour postdose analysis windows
- No rescue medication taken at or before the pain intensity assessment in the 48-hour postdose analysis window.

Participants who are not non-relapsers are classified as relapsers. Relapse criteria include any of the following:

- Rescue medication taken at or before 48 hours postdose (RM=F)
- Mild, moderate, or severe pain intensity at any time point after 2 hours postdose, i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window

- Missing pain intensity at any time point after 2 hours postdose (NC=F), i.e., in the 3, 4, 6, 8, 24, or 48-hour postdose analysis window.

Rescue medication use within 24 hours post dose

- Rescue medication use within 24 hours post dose is defined as: first rescue medication date/time – intervention date/time (in hours) ≤ 24 hours. Participants with first rescue medication date ≤ intervention date +1 day and missing first rescue medication time are excluded.

PGIC overall status improvement over Time

At time point X, participants who meet both of the following criteria are classified as responders (PGIC overall status improvement):

- PGIC overall status improved (defined as very much improved, much improved, or minimally improved) at X, i.e., in the X analysis window
- No rescue medication taken at or before the PGIC assessment in the X analysis window.

At time point X, participants who are not responders are classified as failures. Failure criteria include any of the following:

- Rescue medication taken at or before X (RM=F)
- PGIC overall status not improved (defined as no change, minimally worse, much worse, or very much worse at X
- Missing PGIC overall status at X (NC=F).

Appendix 2.1.2. Rescue Medication = Failure (RM=F) Algorithm

Efficacy assessments that are affected by the RM=F algorithm are pain intensity, nausea status, photophobia status, phonophobia status, and functional disability level.

Let X denote a postdose time point: 15, 30, 45, 60, or 90 minutes; 2, 3, 4, 6, 8, 24, or 48 hours.

If study intervention start date/time is from the eDiary Migraine Report, then it can be linked with its corresponding data at postdose time point X.

For a given assessment at time point X, the objective is to determine whether any rescue medication is taken at or before that assessment, even if the assessment is missing.

Rescue medication taken at or before time point X (RM=F) is defined as either (1) or (2):

1) Rescue medication taken at or before the assessment in the X analysis window. Defined as either of the following if the assessment is non-missing in the X analysis window:
    - (first rescue medication date/time ≤ {eDiary finding date/time for the assessment in the X analysis window}, if first rescue medication time is not missing

- (first rescue medication date ≤ {eDiary finding date for the assessment in the X analysis window}, if first rescue medication date is not missing but time is missing

2) Rescue medication taken at or before the missing assessment in the X analysis window. Defined as either of the following if the assessment is missing in the X analysis window:
   - (first rescue medication date/time – study intervention start date/time) ≤ upper bound of the X analysis window (see Table 2), if first rescue medication time is not missing
   - first rescue medication date ≤ study intervention start date + Y days, if first rescue medication date is not missing but time is missing
     - If X < 24 hours, then Y = 0.
     - If X = 24 hours, then Y = 1.
     - If X = 48 hours, then Y = 2.

Appendix 3. AE Terms

Appendix 3.1. Potential Drug Abuse AEs

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Abnormal sleep-related event
Abulia
Activation syndrome
Acute psychosis
Advanced sleep phase
Adverse drug reaction
Adverse reaction
Affect lability
Affective ambivalence
Affective disorder
Aggression
Agitated depression
Agitation
Alcohol abuse
Alcohol interaction
Alcohol problem
Alcohol use disorder
Alcohol withdrawal syndrome
Alcoholic hangover
Alcoholic psychosis
Alcoholism
Alexithymia
Alice in wonderland syndrome
Altered state of consciousness
Amnesia
Anaesthesia
Anger
Anhedonia
Antisocial behaviour
Apathy
Asocial behaviour
Asthenia
Auditory perseveration
Aura
Autoscopy
Aversion
Behavioural addiction
Binge drinking
Blunted affect
Borderline mental impairment
Boredom

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Bradyphrenia
Brief psychotic disorder with marked stressors
Brief psychotic disorder without marked stressors
Brief psychotic disorder, with postpartum onset
Catatonia
Cholinergic syndrome
Circadian rhythm sleep disorder
Circumstantiality
Clang associations
Clinomania
Confabulation
Confusion postoperative
Confusional arousal
Confusional state
Consciousness fluctuating
Constricted affect
Cotard's syndrome
Crying
Decreased activity
Decreased interest
Deja vu
Delayed sleep phase
Delirium
Delusion
Delusion of grandeur
Delusion of reference
Delusion of replacement
Delusional disorder, erotomanic type
Delusional disorder, grandiose type
Delusional disorder, jealous type
Delusional disorder, mixed type
Delusional disorder, persecutory type
Delusional disorder, somatic type
Delusional disorder, unspecified type
Delusional perception
Dependence
Depersonalisation/derealisation disorder
Depressed level of consciousness
Depressed mood
Depression
Depression suicidal
Depressive delusion
Depressive symptom
Derailment
Derealisation

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Diencephalic syndrome
Disinhibition
Disorganised speech
Disorientation
Dissociation
Dissociative amnesia
Dissociative disorder
Dissociative identity disorder
Disturbance in attention
Disturbance in social behaviour
Dopamine dysregulation syndrome
Dreamy state
Drug abuse
Drug dependence
Drug dependence, antepartum
Drug dependence, postpartum
Drug effect faster than expected
Drug interaction
Drug intolerance
Drug resistance
Drug tolerance
Drug tolerance decreased
Drug tolerance increased
Drug use disorder
Drug use disorder, antepartum
Drug use disorder, postpartum
Drug withdrawal headache
Drug withdrawal syndrome
Drug withdrawal syndrome neonatal
Dysphemia
Dysphoria
Dyssomnia
Egocentrism
Emotional disorder
Emotional distress
Emotional poverty
Erotomanic delusion
Euphoric mood
Exploding head syndrome
Fatigue
Feeling abnormal
Feeling drunk
Feeling jittery
Feeling of despair
Feeling of relaxation

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Feelings of worthlessness
Flashback
Flat affect
Flight of ideas
Formication
Frustration tolerance decreased
Gait deviation
Gait disturbance
Gait inability
Gambling disorder
Glassy eyes
Grandiosity
Hallucination
Hallucination, auditory
Hallucination, gustatory
Hallucination, olfactory
Hallucination, synaesthetic
Hallucination, tactile
Hallucination, visual
Hallucinations, mixed
Hangover
Homicidal ideation
Hyperarousal
Hyperkinesia
Hypersomnia
Hypervigilance
Hypnagogic hallucination
Hypnopompic hallucination
Hypoaesthesia
Hypokinesia
Hypomania
Hyporesponsive to stimuli
Hyposomnia
Hysterical psychosis
Ideas of reference
Idiosyncratic drug reaction
Illusion
Impulse-control disorder
Impulsive behaviour
Inadequate analgesia
Inappropriate affect
Incoherent
Inhibitory drug interaction
Initial insomnia
Insomnia

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Intelligence increased
Intermittent explosive disorder
Intrusive thoughts
Irregular sleep phase
Irregular sleep wake rhythm disorder
Irritability
Jamais vu
Jealous delusion
Judgement impaired
Lack of spontaneous speech
Laziness
Lethargy
Libido disorder
Limited symptom panic attack
Listless
Logorrhoea
Loose associations
Loss of consciousness
Loss of control of legs
Loss of personal independence in daily activities
Magical thinking
Major depression
Malaise
Mania
Medication overuse headache
Memory impairment
Mental impairment
Middle insomnia
Mixed delusion
Moaning
Mood altered
Mood disorder due to a general medical condition
Mood swings
Morose
Narcolepsy
Neglect of personal appearance
Neologism
Neonatal complications of substance abuse
Neuroleptic-induced deficit syndrome
Nicotine dependence
Non-24-hour sleep-wake disorder
Panic attack
Panic disorder
Panic reaction
Paradoxical drug reaction

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Paralogism
Paramnesia
Paranoia
Parasomnia
Paroxysmal perceptual alteration
Pathological doubt
Persecutory delusion
Perseveration
Personality change
Poor quality sleep
Postictal state
Potentiating drug interaction
Poverty of speech
Poverty of thought content
Preictal state
Premenstrual dysphoric disorder
Premenstrual syndrome
Pressure of speech
Pseudodementia
Pseudologia
Psychiatric decompensation
Psychogenic pseudosyncope
Psychomotor hyperactivity
Psychomotor retardation
Psychotic behaviour
Psychotic disorder
Psychotic symptom
Rapid eye movements sleep abnormal
Reactive psychosis
Rebound effect
Rebound psychosis
Schizoaffective disorder
Schizoaffective disorder bipolar type
Schizoaffective disorder depressive type
Schizophrenia
Schizophreniform disorder
Screaming
Seasonal affective disorder
Sedation
Sense of a foreshortened future
Sensory disturbance
Sensory loss
Sensory overload
Sensory processing disorder
Sexually inappropriate behaviour

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Sleep deficit
Sleep disorder
Sleep inertia
Sleep sex
Sleep talking
Sleep terror
Sleep-related eating disorder
Slow response to stimuli
Sluggishness
Social avoidant behaviour
Somatic delusion
Somatic hallucination
Somnambulism
Somnolence
Sopor
Steroid withdrawal syndrome
Stupor
Substance abuse
Substance dependence
Substance use disorder
Substance-induced mood disorder
Substance-induced psychotic disorder
Sudden onset of sleep
Synaesthesia
Syncope
Tachyphrenia
Taciturnity
Tangentiality
Terminal insomnia
Therapeutic product effect decreased
Therapeutic product effect delayed
Therapeutic product effect incomplete
Therapeutic product effect increased
Therapeutic product effect prolonged
Therapeutic product effect variable
Therapeutic product effective for unapproved indication
Therapeutic response changed
Therapeutic response decreased
Therapeutic response delayed
Therapeutic response increased
Therapeutic response prolonged
Therapeutic response shortened
Therapeutic response unexpected
Thinking abnormal
Thought blocking

Table 3. Potential Drug Abuse AE PTs from Clinical Review

PTs
Thought broadcasting
Thought insertion
Thought withdrawal
Time perception altered
Tobacco abuse
Tobacco interaction
Tobacco withdrawal symptoms
Trance
Transient global amnesia
Transient psychosis
Unresponsive to stimuli
Verbigeration
Violence-related symptom
Visual perseveration
Withdrawal syndrome

Table 4. Euphoria-related AE PTs from Clinical Review

PTs
Euphoric mood
Feeling abnormal
Feeling drunk
Feeling of relaxation
Hallucination
Hallucination, auditory
Hallucination, gustatory
Hallucination, olfactory
Hallucination, synaesthetic
Hallucination, tactile
Hallucination, visual
Hallucinations, mixed
Inappropriate affect
Thinking abnormal

Appendix 3.2. Local Irritation AEs

Table 5. PTs in "Application and Instillation Site Reactions" HLT from Clinical Review

PTs
Administration site anaesthesia
Administration site discolouration
Administration site discomfort
Administration site dryness
Administration site dysaesthesia
Administration site erythema
Administration site exfoliation
Administration site haemorrhage
Administration site inflammation
Administration site irritation
Administration site necrosis
Administration site oedema
Administration site pain
Administration site paraesthesia
Administration site reaction
Administration site swelling
Administration site ulcer
Administration site urticaria

Table 6. PTs in "Upper Respiratory Tract Signs and Symptoms" HLT from Clinical Review

PTs
Catarrh
Choking sensation
Dry throat
Increased upper airway secretion
Increased viscosity of upper respiratory secretion
Laryngeal discomfort
Laryngeal pain
Nasal discharge discolouration
Nasal discomfort
Nasal obstruction
Oropharyngeal blistering
Oropharyngeal discolouration
Oropharyngeal discomfort
Oropharyngeal pain
Paranasal sinus discomfort
Rhinalgia
Rhinorrhoea
Sinus headache
Sinus pain

Table 6. PTs in "Upper Respiratory Tract Signs and Symptoms" HLT from Clinical Review

PTs
Sneezing
Throat clearing
Throat irritation
Upper respiratory tract congestion
Upper respiratory tract inflammation
Upper respiratory tract irritation
Upper-airway cough syndrome

Appendix 4. Laboratory Test Toxicity Grades

Laboratory test toxicity grades are assigned using CTCAE or DAIDS criteria as specified in Table 7.

If a value falls into > 1 toxicity grade category, then the highest toxicity grade is chosen.

If fasting status is yes, then fasting toxicity grades are used. Otherwise, nonfasting toxicity grades are used.

Table 7. Laboratory Test Toxicity Grades

	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
Hematology					
Eosinophils *	≤ ULN or ≤ baseline	{> ULN and > baseline} or {> ULN and baseline missing}			
Hemoglobin	≥ LLN	≥ 10.0 to < LLN g/dL; ≥ 6.2 to < LLN mmol/L; ≥ 100 to < LLN g/L	≥ 8.0 to < 10.0 g/dL; ≥ 4.9 to < 6.2 mmol/L; ≥ 80 to < 100 g/L	< 8.0 g/dL; < 4.9 mmol/L; < 80 g/L	
Lymphocytes, high	≤ 4,000/mm3		> 4,000 to ≤ 20,000/mm3	> 20,000/mm3	
Lymphocytes, low	≥ LLN	≥ 800 to < LLN/mm3; ≥ 0.8 to < LLN x 10e9/L	≥ 500 to < 800/mm3; ≥ 0.5 to < 0.8 x 10e9/L	≥ 200 to < 500/mm3; ≥ 0.2 to < 0.5 x 10e9/L	< 200/mm3; < 0.2 x 10e9/L
Neutrophils	≥ LLN	≥ 1,500 to < LLN/mm3; ≥ 1.5 to < LLN x 10e9/L	≥ 1,000 to < 1,500/mm3; ≥ 1.0 to < 1.5 x 10e9/L	≥ 500 to < 1,000/mm3; ≥ 0.5 to < 1.0 x 10e9/L	< 500/mm3; < 0.5 x 10e9/L
Platelets	≥ LLN	≥ 75,000 to < LLN/mm3; ≥ 75.0 to < LLN x 10e9/L	≥ 50,000 to < 75,000/mm3; ≥ 50.0 to < 75.0 x 10e9/L	≥ 25,000 to < 50,000/mm3; ≥ 25.0 to < 50.0 x 10e9/L	< 25,000/mm3; < 25.0 x 10e9/L
White blood cell count	≥ LLN	≥ 3000 to < LLN/mm3; ≥ 3.0 to < LLN x 10e9/L	≥ 2000 to < 3000/mm3; ≥ 2.0 to < 3.0 x 10e9/L	≥ 1000 to < 2000/mm3; ≥ 1.0 to < 2.0 x 10e9/L	< 1000/mm3; < 1.0 x 10e9/L
Serum chemistry					
Albumin	≥ LLN	≥ 3 to < LLN g/dL; ≥ 30 to < LLN g/L	≥ 2 to < 3 g/dL; ≥ 20 to < 30 g/L	< 2 g/dL; < 20 g/L	
ALP *	≤ ULN if baseline ≤ ULN or missing; < 2.0 x baseline	> ULN to ≤ 2.5 x ULN if baseline ≤ ULN or missing;	> 2.5 to ≤ 5.0 x ULN if baseline ≤ ULN or missing;	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing;	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if

Test Name	Grade 0	1	2	3	4
	if baseline > ULN	≥ 2.0 to ≤ 2.5 x baseline if baseline > ULN	> 2.5 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x baseline if baseline > ULN	baseline > ULN
ALT *	≤ ULN if baseline ≤ ULN or missing; < 1.5 x baseline if baseline > ULN	> ULN to ≤ 3.0 x ULN if baseline ≤ ULN or missing; ≥ 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 5.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing; > 5.0 to ≤ 20.0 x baseline if baseline > ULN	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if baseline > ULN
AST *	≤ ULN if baseline ≤ ULN or missing; < 1.5 x baseline if baseline > ULN	> ULN to ≤ 3.0 x ULN if baseline ≤ ULN or missing; ≥ 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 5.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 5.0 x baseline if baseline > ULN	> 5.0 to ≤ 20.0 x ULN if baseline ≤ ULN or missing; > 5.0 to ≤ 20.0 x baseline if baseline > ULN	> 20.0 x ULN if baseline ≤ ULN or missing; > 20.0 x baseline if baseline > ULN
Bicarbonate	≥ LLN	< LLN			
Bilirubin (total) *	≤ ULN if baseline ≤ ULN or missing; ≤ 1.0 x baseline if baseline > ULN	> ULN to ≤ 1.5 x ULN if baseline ≤ ULN or missing; > 1.0 to ≤ 1.5 x baseline if baseline > ULN	> 1.5 to ≤ 3.0 x ULN if baseline ≤ ULN or missing; > 1.5 to ≤ 3.0 x baseline if baseline > ULN	> 3.0 to ≤ 10.0 x ULN if baseline ≤ ULN or missing; > 3.0 to ≤ 10.0 x baseline if baseline > ULN	> 10.0 x ULN if baseline ≤ ULN or missing; > 10.0 x baseline if baseline > ULN
Calcium, high	≤ ULN	> ULN to ≤ 11.5 mg/dL; > ULN to ≤ 2.9 mmol/L	> 11.5 to ≤ 12.5 mg/dL; > 2.9 to ≤ 3.1 mmol/L	> 12.5 to ≤ 13.5 mg/dL; > 3.1 to ≤ 3.4 mmol/L;	> 13.5 mg/dL; > 3.4 mmol/L
Calcium, low	≥ LLN	≥ 8.0 to < LLN mg/dL; ≥ 2.0 to < LLN mmol/L	≥ 7.0 to < 8.0 mg/dL; ≥ 1.75 to < 2.0 mmol/L	≥ 6.0 to < 7.0 mg/dL; ≥ 1.5 to < 1.75 mmol/L	< 6.0 mg/dL; < 1.5 mmol/L
Cholesterol (total)	≤ ULN	> ULN to ≤ 300 mg/dL; > ULN to ≤ 7.75 mmol/L	> 300 to ≤ 400 mg/dL; > 7.75 to ≤ 10.34 mmol/L	> 400 to ≤ 500 mg/dL; > 10.34 to ≤ 12.92 mmol/L	> 500 mg/dL; > 12.92 mmol/L
CK #	≤ ULN	> ULN to ≤ 2.5 x ULN	> 2.5 to ≤ 5 x ULN	> 5 to 10 x ULN	> 10 x ULN
Creatinine	≤ ULN	> ULN to ≤ 1.5 x ULN	{> 1.5 to ≤ 3.0 x ULN} or {> 1.5 to ≤ 3.0 x baseline}	{> 3.0 to ≤ 6.0 x ULN} or {> 3.0 x baseline}	> 6.0 x ULN

	Grade				
Test Name	0	1	2	3	4
eGFR MDRD	≥ LLN	≥ 60 to < LLN mLmin/1.73 m2	≥ 30 to < 60 mL/min/1.73 m2	≥ 15 to < 30 mL/min/1.73 m2	< 15 mL/min/1.73 m2
Glucose, high, fasting @*	< 110 mg/dL; < 6.11 mmol/L	≥ 110 to ≤ 125 mg/dL; ≥ 6.11 to < 6.95 mmol/L	> 125 to ≤ 250 mg/dL; ≥ 6.95 to < 13.89 mmol/L	> 250 to ≤ 500 mg/dL; ≥ 13.89 to < 27.75 mmol/L	> 500 mg/dL; ≥ 27.75 mmol/L
Glucose, high, nonfasting @*	< 116 mg/dL; < 6.44 mmol/L	≥ 116 to ≤ 160 mg/dL; ≥ 6.44 to < 8.89 mmol/L	> 160 to ≤ 250 mg/dL; ≥ 8.89 to < 13.89 mmol/L	> 250 to ≤ 500 mg/dL; ≥ 13.89 to < 27.75 mmol/L	> 500 mg/dL; ≥ 27.75 mmol/L
Glucose, low @	> 64 mg/dL; ≥ 3.55 mmol/L	≥ 55 to ≤ 64 mg/dL; ≥ 3.05 to < 3.55 mmol/L	≥ 40 to < 55 mg/dL; ≥ 2.22 to < 3.05 mmol/L	≥ 30 to < 40 mg/dL; ≥ 1.67 to < 2.22 mmol/L	< 30 mg/dL; < 1.67 mmol/L
Lactate dehydrogenase	≤ ULN	> ULN			
LDL cholesterol, age ≥ 18 years @	< 130 mg/dL; < 3.37 mmol/L	≥ 130 to < 160 mg/dL; ≥ 3.37 to < 4.12 mmol/L	≥ 160 to < 190 mg/dL; ≥ 4.12 to < 4.90 mmol/L	≥ 190 mg/dL; ≥ 4.90 mmol/L	
LDL cholesterol, age > 2 to < 18 years @*	< 110 mg/dL; < 2.85 mmol/L	≥ 110 to < 130 mg/dL; ≥ 2.85 to < 3.37 mmol/L	≥ 130 to < 190 mg/dL; ≥ 3.37 to < 4.90 mmol/L	≥ 190 mg/dL; ≥ 4.90 mmol/L	
Potassium, high	≤ ULN	> ULN to ≤ 5.5 mmol/L	> 5.5 to ≤ 6.0 mmol/L	> 6.0 to ≤ 7.0 mmol/L	> 7.0 mmol/L
Potassium, low	≥ LLN	≥ 3.0 to < LLN mmol/L		≥ 2.5 to < 3.0 mmol/L	< 2.5 mmol/L
Sodium, high	≤ ULN	> ULN to ≤ 150 mmol/L	> 150 to ≤ 155 mmol/L	> 155 to ≤ 160 mmol/L	> 160 mmol/L
Sodium, low	≥ LLN	≥ 130 to < LLN mmol/L	≥ 125 to < 130 mmol/L	≥ 120 to < 125 mmol/L	< 120 mmol/L
Triglycerides	< 150 mg/dL; < 1.71 mmol/L	≥ 150 to ≤ 300 mg/dL; ≥ 1.71 to ≤ 3.42 mmol/L	> 300 to ≤ 500 mg/dL; > 3.42 to ≤ 5.7 mmol/L	> 500 to ≤ 1000 mg/dL; > 5.7 to ≤ 11.4 mmol/L	> 1000 mg/dL; > 11.4 mmol/L
Uric acid (urate) @	< 7.5 mg/dL; < 0.45 mmol/L	≥ 7.5 to < 10.0 mg/dL; ≥ 0.45 to < 0.59 mmol/L	≥ 10.0 to < 12.0 mg/dL; ≥ 0.59 to < 0.71 mmol/L	≥ 12.0 to < 15.0 mg/dL; ≥ 0.71 to < 0.89 mmol/L	≥ 15.0 mg/dL; ≥ 0.89 mmol/L

	Grade				
Test Name	**0**	**1**	**2**	**3**	**4**
Urinalysis					
Urine glucose @*	Negative; ≤ 180 mg/dL	Trace or 1+; > 180 to ≤ 250 mg/dL	2+; > 250 to ≤ 500 mg/dL	3+ or higher; > 500 mg/dL	
Urine protein @*	Negative; < 10 mg/dL	Trace or 1+; ≥ 10 to < 100 mg/dL	2+; ≥ 100 to < 300 mg/dL	3+ or higher; ≥ 300 mg/dL	

@ Graded using DAIDS criteria. All other laboratory tests are graded using CTCAE criteria.
* Modified toxicity grade criteria to correct typos, handle missing baseline, or include additional selection criteria.
For urine glucose, 180 mg/dL is considered the commonly accepted "normal" threshold.[16]
For urine protein, < 10 mg/dL is considered the commonly accepted "normal" threshold.[17]
CK total measured using any method, i.e., fractionated or not fractionated

Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ASE	Asymptotic standard error
AST	aspartate aminotransferase
BMI	body max index
bpm	beats per minute
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
EAS	efficacy analysis set
ECG	electrocardiogram or electrocardiography
EOT	End of Treatment
eCOA	electronic clinical outcome assessment
eDISH	evaluation of drug-induced serious hepatotoxicity
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FAS	full analysis set
FCS	fully conditional specification
FDA	Food and drug administration
HLT	High level term
IP	Investigator product
LFT	liver function test
MBS	most bothersome symptom
MDRD	Modification of Diet in Renal Disease
NA	not applicable
NC=F	Non-Completer=Failure
NC1=F	Non-Completer with missing data at more than 1 time point=Failure
PD	protocol deviation
PGIC	Patient Global Impression of Change
PR	pulse rate
PT	preferred term
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
RM=F	Rescue Medication=Failure

Abbreviation	Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SMQ	Standardized MedDRA Query
SoA	schedule of activities
SOC	system organ class
TBL	Total bilirubin level
TEAE	Treatment emergent adverse event
ULN	upper limit of normal