Statistical Analysis Plan

Interventional, randomized, double-blind, parallel-group, placebo-controlled study of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with dual diagnosis of migraine and medication overuse headache

Eptinezumab

20007A (RESOLUTION)

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Document History

Version	Date	Description of main modifications
1.0	08MAR2024	First final version based on protocol v1.1.
2.0	18OCT2024	Final version to include details for the statistical analysis of data collected during the placebo-controlled period.
3.0	14NOV2024	Final version 3.0 to include updates based on classification meeting minutes before unblinding

Changes Since Version 2.0

Chapter/ Section Number	Chapter/ Section Title	Change & Rationale for Change
12.1.1	Listings of adverse events	Old text: "Listings of adverse events will be sorted by treatment group including participant ID with site ID, Age, Sex, Race, AE number, SOC/PT/investigator term, Infusion reaction (Yes/No), AE start date/time, AE stop date/time/ongoing, date of first IMP infusion, date of the latest IMP infusion prior to the adverse event, time since latest IMP infusion, duration of the adverse event, frequency type (continuous/Intermittent), intensity, seriousness, relationship to IMP (Probable/Possible/Not Related: Specify), action taken with IMP and outcome." New text: "Listings of adverse events will be sorted by treatment group including participant ID with site ID, Age, Sex, Race, AE number, SOC/PT/investigator term, AE start date/time, AE stop date/time/ongoing, date of first IMP infusion, date of the latest IMP infusion prior to the adverse event, time since latest IMP infusion, duration of the adverse event, frequency type (continuous/Intermittent), intensity, seriousness, relationship to IMP (Probable/Possible/Not Related: Specify), action taken with IMP and outcome." Rationale for Change: Since the infusion reaction (Yes/No) in adverse event (AE) listings cannot be confirmed, the infusion reaction column was dropped from all AE listings.

15.4	Patient Global Impression of Change (PGIC)	Old text: "The item is rated on a 7-point scale, where a high score indicate improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse)." New text: "The item is rated on a 7-point scale, where a low score indicate improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse)." Rationale for Change: The item is rated on a 7-point scale, for which a low and not a high score indicates improvement (respectively very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse).
15.10	Treatment Satisfaction Questionnaire for Medicine – 9 Items (TSQM-9)	Old text: Overall satisfaction score in Table 10 Derivation of TSQM-9 Domain Scores "1. Q14*: (Q14-1) × 5/6 (Rescale Q14) 2. [(Q12 + Q13 + Q14*) – 3)]/12*100" New text: Overall satisfaction score in Table 10 Derivation of TSQM-9 Domain Scores "[(Q12 + Q13 + Q14) – 3)]/14*100" Rationale for Change: The TSQM score calculation, due to the rescaling of Q14, based on the original literature, may cause a negative score. Therefore, the score derivation was updated.

List of Abbreviations

AE	adverse events
a.U.	arbitrary unit
AESI	adverse events of special interest
ANCOVA	analysis of covariance
APRS	all-participants-randomized set
APTS	all-participants-treated set
APTS-FU	all-participants-treated-follow-up set
APTS-OL	all-participants-treated-Open-label set
ATC	anatomical therapeutic chemical
BI	brief educational intervention
EPTI	BI + eptinezumab 100 mg
EPTI-EPTI	BI + eptinezumab 100 mg-eptinezumab 100 mg
PBO	BI + placebo
PBO-EPTI	BI + placebo-eptinezumab 100 mg
BMI	body mass index
CGRP	calcitonin gene-related peptide
CIs	confidence intervals
CM	chronic migraine
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EoT	End-of-trial
ePRO	Electronic patient-reported outcome
EQ-5D-5L	Euroqol 5 Dimension – 5 Levels
EU	European Union
FAS	full-analysis set
HADS	Hospital Anxiety and Depression Scale
HCG	human chorionic gonadotropin
HCRU	Health Care Resources Utilization
HIT	Headache Impact Test
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
IMP	investigational medicinal product
MAR	missing at random

MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
MHD	monthly headache day
MI	multiple imputation
ML	maximum likelihood
MMD	monthly migraine day
mMIDAS	modified Migraine Disability Assessment Scale
MMRM	Mixed Models Repeated Measurements
MNAR	missing not at random
MOH	medication overuse headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire, Version 2.1
NSAID	nonsteroidal anti-inflammatory drug
PA	physical activity
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
pMI	placebo-based multiple imputation
PMM	pattern-mixture model
PT	preferred term
REML	restricted maximum likelihood
SAE	serious adverse event
SD	standard deviation
SDS:H	Severity Dependence Scale adapted for headache
SOC	system organ class
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication – 9 items
VAS	Visual Analogue Scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced
WPAI:M	Work Productivity and Activity Impairment Questionnaire, Migraine version

1 Objectives and Endpoints

The trial objectives and endpoints are summarized in Panel 1.

Panel 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective To evaluate the efficacy of eptinezumab as add-on to brief educational intervention (BI) for the prevention of migraine and treatment of medication overuse headache (MOH)	**Primary endpoint:** Change from baseline in the number of monthly migraine days (MMD)s (Weeks 1-4) **Key secondary endpoints:** Change from baseline in MMDs (Weeks 1-12) Change from baseline in the number of monthly headache days (MHD)s (Weeks 1-4) Change from baseline in MHDs (Weeks 1-12) Not fulfilling the International Classification of Headache Disorders (ICHD)-3 diagnostic criteria for chronic migraine (CM) nor MOH (Weeks 1-4) Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12) Change from baseline in average Daily Pain assessment score (Weeks 1-2) Change from baseline in monthly days with acute migraine medication use (Weeks 1-4) Change from baseline in monthly days with acute migraine medication use (Weeks 1-12) **Secondary endpoints:** Not fulfilling the ICHD-3 diagnostic criteria for CM (Weeks 1-4, Weeks 1-12) Not fulfilling the ICHD-3 diagnostic criteria for MOH (Weeks 1-4, Weeks 1-12) Change from baseline in MMDs with use of acute migraine medication (Weeks 1-12) Change from baseline in monthly days with triptan or ergotamine medication use (Weeks 1-12) Change from baseline in monthly days with individual non-opioid analgesics or nonsteroidal anti-inflammatory drug (NSAID) medication use (Weeks 1-12) Change from baseline in monthly days with combination non-opioid analgesics medication use (Weeks 1-12) Migraine on the day after dosing (Day 1)

	Response: ≥50% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) Response: ≥75% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) Response: ≥50% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12) Response: ≥75% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12) Change from baseline in rate of migraines with severe pain intensity (Weeks 1-4, Weeks 1-12) Change from baseline in rate of headaches with severe pain intensity (Weeks 1-4, Weeks 1-12) Patient Global Impression of Change (PGIC) score at Week 4 and Week 12 Most bothersome symptom (MBS) score at Week 12 **Exploratory endpoints:** Complete withdrawal of acute headache medication (Weeks 1-4, Weeks 5-8, Weeks 9-12) Change from baseline in number of days with auras without headache (Weeks 1-4, Weeks 1-12) Change from baseline in duration of severe pain (Weeks 1-4, Weeks 1-12)
Secondary Objectives To evaluate the efficacy of eptinezumab as add-on to BI on health-related quality of life and work productivity	**Secondary endpoints** Change from baseline to Week 4, and from baseline to Week 12 in the Headache Impact Test (HIT-6) total score Change from baseline to Week 4 and from baseline to Week 12 in the modified Migraine Disability Assessment Scale (mMIDAS) total score Change from baseline to Week 4, and from baseline to Week 12 in the Migraine-Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1) sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function) Change from baseline to Week 4, and from baseline to Week 12 in the Euroqol 5 Dimension – 5 Levels (EQ-5D-5L) Visual Analogue Scale (VAS) score Migraine specific Health Care Resources Utilization (HCRU) at Baseline and at Week 12 Change from baseline to Week 12 in the Work Productivity and Activity Impairment Questionnaire, Migraine version (WPAI:M) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment)

	Change from baseline to Week 4, and from baseline to Week 12 in Hospital Anxiety and Depression Scale (HADS) - depression, and anxiety subscale scores Treatment Satisfaction Questionnaire for Medication – 9 items (TSQM-9) score at Week 4 and Week 12
To evaluate the efficacy of eptinezumab during the 12-week open-label extension period	Change from baseline to Week 24 in the HIT-6 total score Change from baseline to Week 24 in the mMIDAS total score Change from baseline to Week 24 in the MSQ v2.1 sub-scores Change from baseline to Week 24 in the EQ-5D-5L VAS score Migraine specific HCRU at Week 24 Change from baseline to Week 24 in the WPAI:M sub-scores Change from baseline to Week 24 in HADS - depression and anxiety subscale scores PGIC score at Week 24 MBS score at Week 24 TSQM-9 score at Week 24 Change from baseline in MMDs (Weeks 13-24) Change from baseline in MHDs (Weeks 13-24) Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 13-24) Change from baseline in monthly days with acute migraine medication use (Weeks 13-24) Change from baseline in average Daily Pain assessment score (Weeks 13-24) Change from baseline in monthly days with triptan or ergotamine medication use (Weeks 13-24) Change from baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 13-24) **Exploratory endpoints:** Change from baseline in number of days with auras without headache (Weeks 13-24) Change from baseline in duration of severe pain (Weeks 13-24)
Exploratory Objectives To investigate the efficacy of eptinezumab as add-on to BI on level of daily physical activity and sleep using a	**Exploratory Endpoints** Change from baseline in passive registration of movement (actigraphy) (Weeks 1-4 and Weeks 1-12, average per 28 days) • Minutes in no motion (0 - <10 a.U.) • Minutes with light motion (10 - <50 a.U.) • Minutes with moderate motion (50 - <100 a.U.) • Minutes with vigorous motion (≥ 100 a.U.) Change from baseline to Week 4 and Week 12 in sleep metrics assessment as assessed by actigraphy (average per 28 days)

wearable digital device (subset)	• Total Sleep Time (minutes per night) • Sleep Efficiency (percentage per night) • Wake After Sleep Onset (minutes per night) • Sleep Onset Latency (minutes per night) All analyses will also be done by week, for example change from baseline to Week 1, baseline to Week 2, and baseline to Week 12.
•To investigate efficacy of eptinezumab as add-on to BI on the level of analgesic dependence	Change from baseline to Week 12 in Severity Dependence Scale adapted for headache (SDS:H) score
Safety Objective •To evaluate the safety and tolerability of eptinezumab	**Safety Endpoints** Adverse events (AEs) Absolute values and changes from baseline in vital signs Potentially clinically significant vital signs changes

2 Investigational Plan

2.1 Overall Trial Design and Plan

This is a phase 4, interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled trial designed to demonstrate the efficacy and safety of add-on eptinezumab treatment to BI, performed at baseline, for the prevention of migraine and treatment of MOH in participants with a dual diagnosis of migraine and MOH.

The 12-week Placebo-controlled Period will be followed by a 12-week Open-label Period where all participants will receive eptinezumab to provide further relief and gain exploratory data on the durability of a potential remission of the MOH and CM. The safety and tolerability of eptinezumab will be also further assessed in this Open-label Period.

The target population for this trial is defined as participants with a dual diagnosis of migraine and MOH and a level of disease activity matching the CM definition, according to the International Headache Society (IHS) ICHD-3 guidelines.[1] Fulfilment of criteria for migraine and MOH will be confirmed via prospectively collected information from the electronic diary (eDiary) during the screening period.

An *eDiary Eligibility Report* will be used to review eDiary data (including baseline headache and migraine days and eDiary compliance) during the 28-day screening period for the eligibility assessment of:

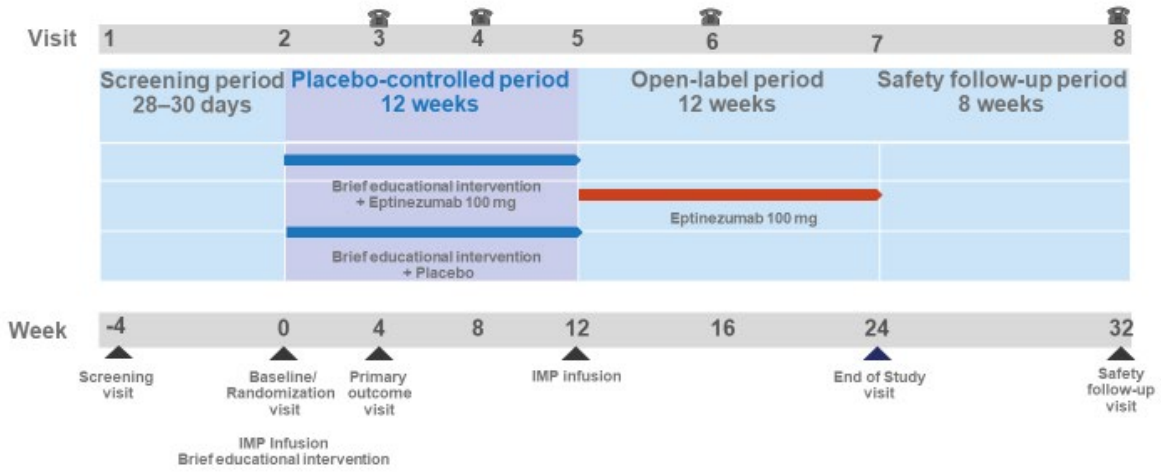
- migraine occurring on ≥8 days and headache occurring on >15 days.
- compliance by entry of headache, acute preventive treatment and aura without headache data for at least 24 of the 28 days following the Screening Visit.

About 570 eligible participants will be randomly allocated via a centralized randomization system to one of the treatment groups: BI and eptinezumab 100mg, or BI and placebo, in a ratio

of 1:1. Randomization will be stratified by country and number of previous preventive treatment failures (≤2; >2) occurring up to 5 years prior to Baseline Visit.

The trial design is presented in Panel 2 and the scheduled trial procedures and assessments are summarized in Appendix 17.1.

Panel 2 Trial Design



IMP = investigational medicinal product

The total trial duration from Screening Visit to Safety Follow-up Contact is approximately 36 weeks and includes a screening period (4 weeks), a Placebo-controlled Period (12 weeks), and an Open-label Period (12 weeks), and a safety follow-up period (8 weeks).

Participants will attend on-site visits at Screening Visit, visits with IMP intravenous (IV) infusions (Baseline Visit and Week 12 Visit), and End-of-trial (EoT) visit at Week 24. All other visits will be conducted as telephone or telemedicine visits.

Participants will complete daily eDiary from Screening Visit until EoT/Withdrawal Visit.

Participants will receive BI and IMP (eptinezumab or placebo) at Baseline Visit during the Placebo-controlled Period and IMP (eptinezumab) at Week 12 Visit during the Open-label Period.

BI is a semi-structured educational conversation with the purpose on helping the participants to stop or reduce the medication overuse. The BI starts with five questions of the SDS:H (including an indication of the participant's willingness and confidence to change his/her medication overuse). Then participant is shown a short-structured scheme bases presentation either on a flip-over or slides with information about MOH and the association between medication overuse and chronic headache. The interview will end with an agreed plan on how to stop or reduce medication overuse (based on self-evaluation questionnaire). The intervention will take approximately 10 minutes to complete and is performed at Baseline Visit before IMP infusion. IMP is administered by IV infusion over 30 minutes (with possibility to extend the IV infusion by 15 minutes).

During the visits with IMP infusion, safety assessments will be performed before and after the infusion. The electronic patient-reported outcomes (ePROs) must be completed in the clinical

site at the visit date prior to the IV infusion. Participants must ensure to complete eDiary recording of headaches prior to the IV infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary).

Participants who interrupt/terminate their IMP IV infusion are encouraged to attend all scheduled trial visits and trial procedures, including the Safety Follow-up to allow for application of treatment policy strategies. Participants who withdraw from treatment with IMP will not be replaced.

The EoT Visit (Visit 7) will be performed at Week 24, 12 weeks after the administration of the second IMP infusion. A Safety Follow-up Contact (Visit 8) will be performed 8 weeks after the EoT Visit. Participants who withdraw from the study, except for those who withdraw their consent or are lost to follow-up, will be asked to attend a Withdrawal Visit as soon as possible and a subsequent Safety Follow-Up Visit 20 weeks after the last administration of IMP. Participants who withdraw the informed consent should complete the safety follow-up and be withdrawn from the study.

Participants in the trial will have access to appropriate medical care in accordance with usual clinical practice after they complete or withdraw from the trial.

3 Definitions

3.1 Definition of Baseline

For the endpoints based on daily recordings in the eDiary, i.e. the migraine, headache, aura without headache and acute migraine medication endpoints, the baseline values will be based on the data recorded daily in the eDiary during the first 28 days following the screening visit.

For the actigraphy endpoints, the baseline values will be based on the data recorded daily by the wearable device during first 28 days following the screening visit.

For all other endpoints, baseline will be defined as the latest available valid measurement taken prior to the administration of IMP.

3.2 Definition of Trial Periods

Classification of concomitant medications and adverse events into trial periods is defined in Section 8, and Section 12.1, respectively. For other data, assessments from the Withdrawal visit and Unscheduled visits will be assigned to a nominal, i.e. scheduled visit (see Section 15.13). The trial consists of the following periods:

- Screening Period (28-30 days): Starts at Visit 1 (End of Week -4) and continues until the beginning of Visit 2 prior to administration of the IMP (End of Week 0).
- Placebo-controlled Period (12 weeks): Starts at the beginning of Visit 2 IMP infusion (End of Week 0) and continues until the beginning of Visit 5 IMP infusion (End of Week 12), or, for the participants with no Visit 5 IMP infusion, until Week 12, or, for the participants withdrawn from the study prior to Week 12 visit, until Week 12 (84±2 days after Visit 2 IMP infusion).
- Open-label Period (20 weeks): Starts at the beginning of Visit 5 IMP infusion (End of Week 12) and continues up to and including the Safety Follow-up visit (Week 32).

The definition of the Placebo-controlled Period implies that for participants in the all-participants-treated-follow-up set (APTS-FU), see Section 4 below for definition, adverse events and concomitant medications reported after withdrawal in the Placebo-controlled Period but before Week 12, will be allocated to the Placebo-controlled Period.

For the APTS-FU patients, the safety assessments, and concomitant medications data subsequently collected at the Safety Follow-up visit will be reported separately in data listings.

For patients who enter the Open-label Period, the safety assessments and concomitant medications data collected at the Safety Follow-up visit will be presented together with the safety assessments and concomitant medications data collected during the Open-label Period.

3.3 Definition of Withdrawal

Withdrawal from study

The group of participants who withdraws from the study in the Placebo-controlled Period prior to receiving the IMP in the Open-label Period will be described as withdrawals from the study during the Placebo-controlled Period. The complementary group will be described as having completed the Placebo-controlled Period.

Similarly, for the Open-label Period, the group of participants who withdraw from the study before EoT visit (end of Week 24) after receiving IMP in the Open-label Period will be described as withdrawals from the study during the Open-label Period and the complementary group will be described as having completed the Open-label Period.

Withdrawal from treatment

Withdrawal from the treatment in the Placebo-controlled Period or the Open-label Period is not possible because IMP is only administrated once at Baseline/Randomization visit or Visit 5. Note that the infusion interruptions or terminations before full dose is received are not related to withdrawal.

3.4 Definition of End-of-trial

The end of the trial for an individual participant is defined as the last protocol-specified contact with that participant.

The overall end of the trial is defined as the last protocol-specified contact with the last patient in the trial.

3.5 Definition of Planned versus Actual Treatment

Participants will receive either BI + eptinezumab 100 mg (EPTI), or BI + placebo (PBO) in the Placebo-controlled Period and eptinezumab 100 mg in the Open-label Period.

Planned treatment is defined as the treatment a participant was randomized to.

Actual treatment is defined as the treatment a participant actually received during the trial.

The term treatment group is used to denote which treatment (EPTI vs. PBO) participants received in the Placebo-controlled Period and in the Open-label Period. The term treatment sequence will be used to denote the treatment groups arising by combining the treatment received in the Placebo-controlled Period and eptinezumab 100 mg received in the Open-label

Period, i.e. the 2 groups are: PBO-eptinezumab 100 mg (PBO-EPTI) and EPTI-eptinezumab 100 mg (EPTI-EPTI).

For reporting purposes, the following will be summarized by planned treatment:

- Disposition
- Demographics and baseline characteristics
- Concomitant medication
- eDiary compliance
- Efficacy

And the following will be summarized by actual treatment:

- Exposure
- Adverse events
- Vital signs

Unless otherwise specified, safety data and concomitant medications data listings will be displayed using actual treatment sequence and other data listings will be displayed using planned treatment sequence.

3.6 Definition of Migraine, Headache Days

For the purpose of endpoint derivations, the following definitions of migraine and headache days will be used:

In this trial, the term headache will encompass both headaches and migraine headaches. Migraine headaches (henceforth simply referred to as “migraines”) are a subgroup of headaches with characteristics outlined below (Section 3.6.1). Using this definition, all migraines are headaches but not all headaches are migraines.

Headaches will be self-reported by the participant using an electronic headache diary on a daily basis from the time of screening until EoT/Withdrawal Visit. The eDiary is split into three parts: the headache diary, the aura without headache diary and the evening diary. The headache diary is the part of the eDiary where the start and stop date and times of experienced headaches are recorded along with headache characteristics and the intake of acute headache/migraine medication. Headache items will be assessed with a yes/no response; severity of pain will be rated as mild, moderate, or severe.

The headache diary is available all day. Participants are required to provide information on headache characteristics including associated symptoms and acute migraine medication intake on each day of an (ongoing) headache (either when a headache has ended or during the evening routine if the headache is ongoing).

The aura without headache diary is the part of the eDiary where data is collected on whether the participant experienced an aura without a headache and whether and what kind of acute headache medications were taken in relation to this event.

The evening diary is the part of the eDiary, that participants are expected to complete each evening. It collects data on acute migraine medication that was taken preventively and triggers the evening routine including the headache and aura without headache diaries.

Panel 3 IHS ICHD-3 Guidelines for Migraine

<table>
<tr>
<th>1.1 Migraine without aura</th>
<th>1.2 Migraine with aura</th>
</tr>
<tr>
<td>A. At least five attacks fulfilling criteria B to D

B. Headache attacks lasting 4 to 72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (for example walking or climbing stairs)

D. During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis</td>
<td>A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:
1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:
1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5–60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<th colspan="2">1.3 Chronic migraine</th>
</tr>
<tr>
<td colspan="2">A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B to D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≥8 days/month for >3 months, fulfilling any of the following:
1. criteria C and D for 1.1 Migraine without aura
2. criteria B and C for 1.2 Migraine with aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</table>

3.6.1 Migraine Day

The migraine day definition is based on the IHS guidelines[1] for controlled studies of preventive treatment of migraine in adults.

During the trial, a day with a headache can be here defined as a migraine day if the headache belongs to any subgroup of headaches.

(1) A headache lasts at least 30 minutes and meets the following two criteria:
- At least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity
- During the headache the participant had at least one of the following:
  - nausea
  - vomiting
  - photophobia and phonophobia

(2) A headache lasts at least 30 minutes and where the participant had an aura with the headache

(3) A headache lasts at least 30 minutes and meets two of the following three criteria:
- lasting 4 hours
- At least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity
- During the headache the participant had at least one of the following:
  - nausea
  - vomiting
  - photophobia and phonophobia

(4) A day with a headache that is successfully treated* with a migraine specific treatment, as classified in the master medication list.

(5) A day with an aura without a headache with medication taken

Data on characteristics of a headache will be collected in the eDiary for each day of the headache. For each headache it will be determined whether a headache is a migraine or a non-migraine headache based on the total headache duration and the pooled symptoms over all days of the headache. All days on which this headache occurs will then be classified as a migraine day if the headache qualifies as a migraine headache.

If a headache lasts ≥72 hours, the days will still be counted as *headache days* or *migraine days* as aligned with the IHS guidelines.[1]

Further details on the definitions:

* If participants are taking acute migraine medication, the following questions are captured in the headache diary: "*Did you take any medications to treat this headache today?*" and "*Did at least one of the medications you took today successfully treat your headache?*" Only if both are affirmed will the treatment of the headache be considered "successful".

For exploratory analyses, two alternative definitions of a migraine day will be applied:

(1) a day will be qualified as a migraine day based on the symptoms and duration of the headaches occurring on that specific day only.

(2) if a headache is lasting several days, all days on which this headache occurs will then be classified as a migraine day if the headache qualifies as a migraine using the approach number 1) for at least one of these days.

3.6.2 Headache Day

A headache day is defined as a day with a headache that lasts ≥30 minutes or that meets the definition of a migraine day.

Note: In case of a headache with start date/time and end date/time spanning multiple calendar days, all the calendar days overlapping with the ongoing headache (regardless of duration) will be counted as a headache day (or a migraine day if the headache qualifies as a migraine headache).

If a headache lasts ≥72 hours, the days will still be counted as *headache days* or *migraine days* as aligned with the IHS guidelines.

For the exploratory analyses corresponding to using the alternative definitions 1) and 2) for a migraine day as outlined in the previous section, a headache day is defined as a day on which the headache lasts ≥30 minutes on that specific day or that meets the definition of a migraine day.

3.7 Definition of a Reported eDiary Day and a Missing eDiary Day

A reported eDiary day is a day where at least one of the following pieces of information are available:

- A headache event is reported to take place and the participant has recorded the daily symptoms for at least one of the days spanned by this headache
- The headache eDiary has been completed, and it has been confirmed that no headaches happened on this day
- Aura without headache diary is reported with a taken medication

A missing eDiary day is defined as a day that is not a reported eDiary day.

3.8 Definition of Migraine Attack and Headache Episode

3.8.1 Migraine Attack

A migraine that fulfils the criteria for a migraine, is also referred to as a migraine attack. A migraine attack can last for a single day or for multiple days. Two migraine attacks are considered distinct, if they are split by a time gap where the participant had no headache at all. A time gap can be of any duration, i.e. two attacks are distinct as soon as there is a period of time of

any duration in between where the participant did not have a headache. An aura without headache with a taken medication is also considered a migraine attack.

3.8.2 Headache Episode

A non-migraine headache that lasts ≥30 minutes or a migraine headache, is also referred to as a headache episode. A headache episode can last for a single day or for multiple days. Two headache episodes are considered distinct, if they are split by a time gap where the participant had no headache at all.

3.9 Definition of Chronic Migraine and Medication Overuse Headache based on eDiary data

Participants who have a diagnosis of CM and MOH by IHS ICHD-3 guidelines at the Screening Visit and at the Baseline prior to the IMP will be randomized and dosed. Also, several endpoints are based on whether or not the participant fulfils the CM or MOH criteria during a specific post-baseline 4-week period using the following definition.

3.9.1 Definition of CM based on eDiary data

To evaluate whether a participant fulfils the CM criteria during a specific post-baseline 4-week period, we will use the eDiary data for that month (28-day period) and follow the steps below.

Step 1: Count number of monthly headache days.

If MHD ≥15 days in the reported month, then continue to Step 2.

Step 2: Count number of monthly migraine days
At least 8 monthly migraine days using definition of migraine day from 3.6.1 are needed for a participant to fulfil the CM criteria.

3.9.2 Definition of MOH during the trial

Panel 4 IHS ICHD-3 Guidelines for MOH

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder

B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

C. Not better accounted for by another ICHD-3 diagnosis

Regular overuse is defined either on:

- 10 days of use/month or more for >3 months of ergotamine, triptan, opioid (butalbital in US), or combination of analgesics
- 15 days of use/month or more for >3 months of non-opioid analgesics (paracetamol [acetaminophen], acetylsalicylic acid, NSAIDs)

In Panel 4 above, the IHS ICHD-3 Guidelines for MOH are stated and used to confirm the MOH diagnosis at the screening visit.

During the trial, to evaluate whether a participant continue to overuse acute migraine medication, the eDiary data will be used for a specific post-baseline 4-week period (28-day period) only and the steps below will be followed:

Check acute migraine medication overuse in the reported month.

Count the number of days on which a medication was taken to treat a headache for each pre-defined acute migraine medication in the reported month (28-days period).

If the participant meets any of the following criteria in the reported month, the participant is considered as overusing acute migraine medication, used as "MOH" in the endpoint definitions. N is the number of monthly days.

- N≥10 days with either ergotamine, or N≥10 days with triptan
- N≥10 days with combination of two or more drug classes among ergotamine, triptan, opioid analgesic and non-opioid analgesics
- N≥10 days on which combination analgesics are taken.
- N≥15 days on which a non-opioid analgesic (paracetamol, acetylsalicylic acid, NSAIDs, analginum, antipyrine, tolfenamic acid) is taken. The overuse could be with a single non-opioid analgesic or with several of them.

4 Analysis Sets

The following analysis sets will be used to analyse and present the data:

- *all-participants-screened set (APSS)*
- *all-participants-randomized set* (APRS) – all randomized participants
- *all-participants-treated set* (APTS) – all participants in the APRS who received an infusion of the IMP in the Placebo-controlled Period
- *full-analysis set* (FAS) – all participants in the APTS who had a valid baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
- *all-participants-treated-open-label set* (APTS-OL) – all participants in the APRS who received an infusion of the IMP in the Open-label Period
- *all-participants-treated-follow-up set* (APTS-FU) - All participants in the APTS who are not in the APTS-OL, and who have data collected from the Safety Follow-up visit.

All data from the Placebo-controlled Period will be cleaned and the trial database for the Placebo-controlled Period will be locked when all participants have either completed or been withdrawn from the Placebo-controlled period. The participants and data will be classified into the analysis sets (APRS, APTS, and FAS) at a *Classification Meeting* held after the trial database for the Placebo-controlled Period has been released.

Data will be unblinded after the *Classification Meeting* for the sponsor and CRO functions involved in performing the analysis. All analyses specified in the SAP for data collected in the

Placebo-controlled Period will be performed. Sponsor and CRO functions that are in contact with the trial site staff, as well as clinical site staff and participants will remain blinded to individual participant treatment assignment through the end of the trial.

After all participants have completed the Open-label Period, the trial database for the full trial will be cleaned and locked. The participants and data will be classified into the analysis sets (APTS-OL and APTS-FU) according to these definitions. The defined population sets will be reviewed at a second *Classification Meeting* held after the full trial database has been released. The CTR will be issued after the end of the full trial completion.

Unless otherwise specified, the FAS will be used for all efficacy analyses in the Placebo-controlled Period, and the APTS will be used for all safety analyses in the Placebo-controlled Period, while the APTS-OL will be used for the safety and efficacy analysis of the Open-label Period. Relevant safety outputs for data collected at the Safety Follow-up visit for the APTS-FU will be listed.

5 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables and counts and, if relevant, percentages will be presented for categorial variables.

Mean, median and confidence intervals (CIs) will be presented with one more decimal place than the individual values. SD will be presented with two more decimal places than the individual values. Minimum and maximum will be presented with the same number of decimal places as the individual values. P-values will be presented with four decimal places, ratios with three decimal places and test statistics with two decimal places. Percentages will have one decimal place.

Unless otherwise specified, data listings for the Placebo-controlled Period will include site, treatment group, participant screening number, sex, age, and race. For the Open-label Period, the listings will include treatment sequence in the Open-label Period in addition to the variables included in listings for the Placebo-controlled Period.

6 Participant Disposition

6.1 Summary of Participant Disposition

The summary of participant disposition will be presented for each country and overall. Participant disposition will be summarized separately for the Placebo-controlled Period and the Open-label Period, respectively, and will present participant disposition by treatment group and in total in the former case, and by treatment sequence and in total in the latter.

The summary for the Placebo-controlled Period will include number of randomized participants, number of treated participants during the period, number of participants who completed the period or withdrew from study during the period, primary reason for withdrawal from the study, and all reasons for withdrawal from the study. Percentages will be provided based on the APRS.

The summary for the Open-label Period will include number of treated participants during the period, number of participants who completed the period or withdrew from study during the

period, primary reason for withdrawal from the study, and all reasons for withdrawal from the study. Percentages will be provided based on the APTS-OL.

The summary of analysis sets defined in the Section 4 will include number of participants screened, number of screen failures, number of participants in APRS, APTS, FAS, APTS-OL and APTS-FU. Percentages will be provided based on the APRS.

Two listings with randomization and screening number information will be provided. One listing, sorted by randomization number, containing randomization number, participant screening number and treatment group information, and the other should be sorted by participant screening number showing screening number, randomization number, and treatment group information.

A listing with important protocol deviations containing patient ID, site ID, deviation subtype and deviation description will be provided.

6.2 Withdrawals

Participants who withdrew from the study will be listed for the Placebo-controlled and the Open-label Period, respectively. The listings will be presented by treatment group and include participant ID with site ID, Age, Sex, Race, date of withdrawal from study, primary reason for withdrawal, and all reasons for withdrawal with specification information. For the listing for the Open-label Period treatment sequence will be used to replace the treatment group.

Kaplan-Meier plots of time to withdrawal from the study will be presented by treatment group for the Placebo-controlled Period based on APTS and by treatment sequence for the Open-label Period based on APTS-OL. The time will be calculated from the date of first dose of IMP to the date of withdrawal in the Placebo-controlled Period, and from the date of the Open-label Period IMP to the date of withdrawal in the Open-label Period, respectively. Participants will be censored at the end of the Placebo-controlled Period, and the Open-label Period, respectively.

7 Demographics and Baseline Characteristics

Demographics including sex, age, race, ethnicity and baseline body measurements including height, weight and body mass index (BMI) will be summarized by treatment group for APTS. Baseline disease characteristics will be summarized by treatment group for APTS. Baseline efficacy variables (eDiary or ePROs) will be summarised by treatment group for FAS.

7.1 Demographics and Baseline Characteristics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics:

- age (years)
- weight (kg)
- height (cm)
- BMI (kg/m^2)

The number and percentage of participants will be provided for the following categorical variables:

- sex (Male vs. Female)

- race (White, Black, Asian, Other, Not Stated/Unknown)
- ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Stated/Unknown)
- country

7.2 Baseline Disease Characteristics

Baseline disease characteristics comprise of the follows:

- age at first diagnosis of migraine (Years)
- duration since first migraine diagnosis (Years)
- age at first diagnosis of MOH (Years)
- time since first diagnosis of MOH (Years)
- type of acute headache treatment taken during the screening period (triptan, ergotamine, opioid analgesics, combination of analgesics, non-opioid analgesics)
- type of preventive headache medication taken during the screening period
- participant suffered from aura (Yes/ No): if yes, which aura symptoms
- participant ever experienced aura without headache (Yes/ No) based on migraine history
- number of female participants with migraine started before or after menarche
- number of males with migraine started before or after puberty
- start of migraine was related to any event (Yes/ No).

7.3 Baseline Efficacy and Pharmacoeconomic Characteristics

The eDiary reported baseline headache characteristics during the screening period will be summarized as follows:

- number of MMDs
- number of MHDs
- number of monthly migraine attacks
- number of monthly headache episodes
- proportion of migraine attacks with severe pain intensity
- proportion of headache episodes with severe pain intensity
- average length of migraine attacks (Hours)
- average length of headache episodes (Hours)
- number of MMDs with use of acute migraine medication
- number of monthly days with use of acute migraine medication.

The ePROs baseline variables will be summarized as follows:

- HIT-6 total score: summarized as a continuous variable and as a categorical displaying the percentage and counts of the life impact categories (see Section 15.2)
- mMIDAS total score
- number and percentage of MBS symptom chosen
- MSQ v2.1 domain scores (Role Function Restrictive, Role Function Preventive, Emotional Function)
- HADS sub-scores (Depression, Anxiety)
- EQ-5D-5L VAS score
- WPAI:M sub-scores (Absenteeism, Presenteeism, Work Productivity Loss, Activity Impairment)
- HCRU items (0,1,2,3, …, i.e. presented as a discrete variable)
    - number of visits to a family doctor/general practitioner
    - number of visits to a specialist
    - number of emergency department visits
    - number of hospital admissions
    - total number of overnight hospital stays

7.4 Medical History

Medical history including significant and relevant past medical, neurological, and psychiatric disorders except for migraine history and medication overuse headache history will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA, Version 25.0 or later) and summarized separately in past and concurrent disorders.

A past medical, neurological, or psychiatric disorder is a disorder that ended prior to the Screening Visit. A concurrent medical, neurological, or psychiatric disorder is a disorder that is ongoing at the Screening Visit. Past and concurrent disorders will be summarized by system organ class (SOC) and preferred term (PT) by treatment group based on APTS.

8 Treatments and Medications

8.1 Recent and Concomitant Medications

Recent and concomitant medication is any medication other than the IMP that is taken during the trial, up until the Safety Follow-up Contact, including during the screening period. Recent and concomitant medication will be coded using the *WHO Drug Dictionary Enhanced* (WHO-DDE).

Medications will be classified according to the start and stop dates and summarized by anatomical therapeutic chemical (ATC), generic drug name and treatment group. Handling of missing or incomplete dates is specified in Section 15.14.4.

The following categories will be used:

- Prior medications: Medications taken prior to the first IMP infusion.
- Concomitant medications taken during the Placebo-controlled Period: Medications with a start date prior to Visit 5 and an end date that is either missing or at or after the date of first IMP infusion, medications with a missing start date and an end date at or after the date of first IMP infusion, and medications missing both stop and start dates. For participants in the APTS-FU set, concomitant medications reported after withdrawal in the Placebo-controlled Period but before Week 12, will be allocated to the Placebo-controlled Period, see also Section 3.2.
- Concomitant medications during the Open-label Period: Medications with a start or stop date at or after the date of visit 5 IMP infusion and medications where both start and stop date are completely missing. Ongoing medications are also included, as well as medications with a completely missing stop date.
- Concomitant medications reported in connection to the Safety Follow-up visit (applicable only for the APTS-FU analysis set if information on any such medications have been collected): Medications with a start or stop date at or after Week 12.

The tables for prior medication, concomitant medications during the Placebo-controlled Period will be based on APTS, and concomitant medications during the Open-label Period will be based on the APTS-OL. The prior and concomitant listing will be provided with an identified variable to show whether the medication is prior, concomitant during the Placebo-controlled Period, or concomitant during the Open-label Period.

All disallowed medications during the Placebo-controlled Period will be listed based on the APTS. The listing will include the generic drug name, the duration, the start and end dates, and dosing information. A similar listing will be provided for the participants taking disallowed concomitant medications during the Open-label Period based on the APTS-OL.

8.2 Acute Migraine Medications

The eDiary reported medications will be handled separately. The number of participants taking each of the medication types will be presented for each 4-week interval in the Placebo-controlled Period by treatment group and in the Open-label Period by treatment sequence.

8.3 Migraine Preventive Medications

Prior and concomitant migraine preventive medications used will be collected in the eCRF.

8.3.1 Prior Preventive Medication Treatment Failure

Migraine preventive medication treatment failure will be summarized by treatment group for APTS in the Placebo-controlled Period.

Prior preventive treatment failures within 5 years prior to the screening visit will be summarized as follows:

- number of participants with prior preventive treatment failures (≤2; >2)
- total number of treatment failures (1,2,3, …, i.e. presented as a discrete variable)

- medication (Propranolol, Metoprolol, Topiramate, Amitriptyline, Flunarizine, Candesartan, Valproate, Divalproex, Botulinum toxin A, Botulinum toxin B, Timolol, Other: Specify)
- type of treatment failure (Lack of Efficacy, Safety/Tolerability, Contraindication).

8.4 Substance Use

Substance use (alcohol, tobacco, caffeine, marijuana consumption) throughout the trial will be collected at all visits until the Week 12 Visit/Withdrawal Visit (if the participant withdraws during the placebo-controlled period). Substance use will be summarized by treatment group and visit based on APTS.

9 Exposure

All randomized participants are expected to receive one single infusion of the IMP after BI in the Placebo-controlled Period and one infusion of the IMP in the Open-label Period. For each infusion visit, information related to infusion will be summarized by actual treatment group for the Placebo-controlled Period and by actual treatment sequence in the Open-label Period:

- BI completed as planned
- infusion completed as planned
- infusion temporarily interrupted
- infusion lasted longer than 30 (+15) minutes
- duration of infusions (includes duration of any infusion interruptions)
- duration of temporary interruptions.

All infusion data will be listed for each period separately. Additionally, treated participants whose infusion took more than 45 minutes and participants who had their infusion interrupted will be listed by treatment group, infusion start date/time and end date/time, infusion related reactions, and reasons if any.

The summaries will be based on the APTS and APTS-OL, respectively.

10 eDiary Compliance

For the Screening period, the Placebo-controlled Period and the Open-label Period, the rate of days where the eDiary has been missed within each 4-week interval will be summarized and presented by 4-week interval and treatment group/treatment sequence. Furthermore, the number of participants missing 7 days or more and 14 days or more in a 28-day period will be presented by 4-week interval and treatment group/treatment sequence.

The summaries will be based on the FAS for the Placebo-controlled Period and based on APTS-OL for the Open-label Period.

11 Efficacy

11.1 General Efficacy Analysis Methodology

All the tables and graphs will be presented by treatment group for the Placebo-controlled Period and by treatment sequence for the Open-label Period. Unless otherwise specified, all the efficacy

analyses for the Placebo-controlled Period will be based on the FAS and all the efficacy analyses for the Open-label Period will be based on the APTS-OL.

All the statistical tests of the efficacy endpoints will be two-sided tests performed at the 5% significance level and all CIs will be 95% CIs, unless otherwise specified. Details of the imputations used for the eDiary data can be seen in the rules for handling missing data described in Section 15.14.1. Only descriptive summaries will be presented for the efficacy analyses for the Open-label Period.

11.2 Testing Strategy

In all statistical tests, the null hypothesis of equal treatment effect in the two treatment groups will be tested against the two-sided alternative hypothesis of different treatment effect in the two treatment groups. The testing will be done hierarchically, in a sequence of a maximum number of 9 steps where the different null hypotheses are tested until an endpoint fails to reach significance. For each step in this sequence, the treatment effect will be tested using a two-sided test on a 5% significance level and testing will only continue to the next step if all prior effects in the hierarchy were found to have p-values below the specified significance level, thus ensuring protection of the type 1 error.

Step 1
Test the primary endpoint change from baseline in the number of MMDs (Weeks 1-4) for EPTI compared to PBO, using a significance level of 0.05.

Step 2

Test the key secondary endpoint change from baseline in the number of MMDs (Weeks 1-12) for EPTI compared to PBO, using a significance level of 0.05.

Step 3
Test the key secondary endpoint change from baseline in the number MHDs (Weeks 1-4) for EPTI compared to PBO, using a significance level of 0.05.

Step 4
Test the key secondary endpoint change from baseline in the number MHDs (Weeks 1-12) for EPTI compared to PBO, using a significance level of 0.05.

Step 5
Test the key secondary endpoint not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4) for EPTI compared to PBO, using a significance level of 0.05.

Step 6
Test the key secondary endpoint not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12) for EPTI compared to PBO, using a significance level of 0.05.

Step 7
Test the key secondary endpoint change from baseline in average Daily Pain assessment score (Weeks 1-2) for EPTI compared to PBO, using a significance level of 0.05.

Step 8
Test the key secondary endpoint change from baseline in monthly days with acute migraine medication use (Weeks 1-4) for EPTI compared to PBO, using a significance level of 0.05.

Step 9
Test the key secondary endpoint change from baseline in monthly days with acute migraine medication use (Weeks 1-12) for EPTI compared to PBO, using a significance level of 0.05.

11.3 Analysis Methodology for the of Primary Endpoint

11.3.1 Primary Estimands

The primary estimand will be the mean difference in change from baseline in MMDs (Weeks 1-4) in participants with a dual diagnosis of migraine and MOH treated with add-on eptinezumab treatment to BI and add-on placebo treatment to BI, regardless of use of preventive migraine treatment, assuming other anti-CGRP treatment is not available and regardless of infusion interruption or termination before full dose is received.

A summary of the primary estimand including intercurrent events and strategies can be found below in Table 1 and Table 2.

Table 1 Intercurrent Event Types

Label	Intercurrent Event Type
ICE1 (new preventive medication)	Initiation of a new preventive migraine medication other than anti-CGRP treatment, during the trial period
ICE2 (anti-CGRP medication)	Use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication
ICE3 (interruption/termination of infusion)	Interruption/termination of infusions

Table 2 Primary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Primary Objectives	To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH
Estimand Label	**Estimand 1 (Primary)**
Estimand Description	The mean difference in the change from baseline in MMDs (Weeks 1-4) between participants on EPTI and PBO regardless of the use of preventive migraine medication and interruptions/terminations of infusions, assuming other anti-CGRP treatment is not available.
Target Population	Participants who suffer from migraine and MOH and who fulfil the inclusion and exclusion criteria.
Treatment Conditions	Trial arm: BI and eptinezumab 100 mg Control arm: BI and placebo
Endpoint	Change from baseline in the number of MMDs across weeks 1-4

Primary Objectives	To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH
Estimand Label	**Estimand 1 (Primary)**
Population Level Summary	The mean difference in the change from baseline in MMDs (Weeks 1-4) between participants on EPTI and PBO.
ICEs and Strategies	
ICE1 (new preventive medication)	Treatment policy
ICE2 (anti-CGRP medication)	Hypothetical
ICE3 (interruption/termination of infusion)	Treatment policy
Rationale	A treatment policy strategy is used to estimate the treatment effect irrespective of new preventive migraine medication other than anti-CGRP treatment initiation and interruption/termination of infusions during trial period to reflect clinical practice. Under the assumption of less use of preventive migraine treatment in the eptinezumab group compared to the placebo group, this is considered to be a conservative approach. A hypothetical strategy is used to handle use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication. This will better reflect clinical practice, since it is not standard practice to prescribe two different anti-CGRP treatments simultaneously.

11.3.2 Primary Analysis of the Primary Endpoint

The primary estimand will be estimated using MMRM described below.

Changes from Baseline in the number of MMDs at the 4-week intervals (Weeks 1-4, Weeks 5-8, Weeks 9-12) will be analysed using a restricted maximum likelihood (REML)-based MMRM approach. The analysis will be performed using all available monthly scores in the trial derived as specified in Section 15.1.1.

The model will include the following fixed effects: baseline number of MMDs as a continuous covariate, treatment group (EPTI versus PBO), month (Month 1: Weeks 1-4; Month 2: Weeks 5-8; Month 3: Weeks 9-12), country, and previous treatment failures (≤2; >2) as factors. The interaction terms treatment-by-month and previous treatment failures (≤2; >2) by month as well as number of MMDs at baseline-by-month will be included. An unstructured covariance matrix will be used to model the between and within-participant covariance. If, unexpectedly, this analysis fails to converge, the following variance structures will be tried out, in the following

order: first-order ante-dependence, heterogenous compound symmetry, compound symmetry, and the first to converge will be applied. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The mean differences between EPTI and PBO estimates will be presented with p-values and 95% CIs. A least square mean change from baseline figure will show the comparison between two treatment groups by month. The primary comparison will be the contrast between EPTI and PBO at Weeks 1-4. If the two-sided p-value for this comparison is <0.05 and favours eptinezumab, the primary analysis has shown a statistical significance favouring EPTI over PBO. The primary endpoint analysis will follow the testing strategy described in Section 11.2.

11.3.3 Rationale for Selected Analysis Method for the Primary Endpoint

The MMDs are considered continuous data, and they are analysed using methods based on observations following a normal distribution. Given the repeated observation of normally distributed data, an MMRM analysis using all available data has been chosen for the primary analysis. Covariates are included in the model based on an approach including key factors that enable an evaluation of the treatment effect over time (month, treatment), factors representing trial design features (stratification variables country and previous treatment failures, where the stratification variables will indicate the strata used for randomisation), and the baseline MMD score to account for differences in baseline MMDs and its predictive ability. Including time as a factor and an unstructured covariance matrix results in a flexible model that does not make strong assumptions about how the primary endpoint develops over time and provides robust estimation, even under some deviation from the assumption of normality.

The use of MMRM combined with the rules for handling missing data in this set-up allows for inclusion of the majority of the participants, even if they only have limited data observed.

11.3.4 Sensitivity Analyses of the Primary Endpoint

11.3.4.1 Assessing the impact of missing data using a pattern-mixture model

A sensitivity analysis using the placebo-based multiple imputation (pMI) method to assess the robustness of the conclusions for this endpoint with respect to the missing data will be conducted. Specifically, an analysis will be performed using a pattern-mixture model (PMM), in which the remaining missing data after application of the prorating rule, see Section 15.1.1, will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the PBO group.[2] As the missing not at random (MNAR) strategy chosen will impute all missing data for participants treated with eptinezumab, as if they were treated with placebo, this is considered to be a conservative approach.

200 simulations will be performed to generate the datasets that will be analysed using the model described in Section 11.3.2. These analyses will be combined using Rubin's rule to form a unique point estimate and standard error, taking into account the uncertainty of the imputation.

11.3.4.2 Assessing the impact of missing data using a tipping point analysis

To further evaluate the potential impact of missing data, a multiple imputations (MI) approach will be used to impute the missing data for all three 4-week post-baseline periods in the Placebo-controlled Period using a tipping point analysis, where the robustness of the results under

increasing deviations from missing at random (MAR) for the missing observations will be assessed.

After the use of prorating, the remaining missing data for each month will firstly be imputed through standard MI under MAR assumption. In addition, the imputed data for MMDs on eptinezumab for each 4-week post-baseline period will be adjusted by applying a range of deviations based on delta (δ) and the estimated effects for EPTI and PBO for each 4-week post-baseline period from primary analysis as follows:

$$\text{EPTI} + \delta \cdot (\text{PBO} - \text{EPTI}),$$

where δ will take values 0%, 10%, 20%, 30%, …

Thus, the estimated effect will start from an assumption of the effect being similar to the effect in other participants treated with EPTI, and then stepwise worsen, with δ =100% being an assumption of participants with missing data having a similar effect as placebo. The value of δ will be increased until the p-value > 0.05, or until the limit for the worst score possible for the missing data has been reached. In case of monthly migraine days, the score cannot be worse than 28 days with migraine out of 28 days observed. The method used for imputation, analysis of data and combination of results from analyses will match the pMI method described above (same seed numbers will also be used), except for the assumed effect for the EPTI group which will be as described in this section.

11.3.5 Subgroup Analysis for Primary Endpoint

Subgroup analyses will be performed using the model specified in Section 11.3.2 on the set of participants included in the subgroup.

The subgroups that will be investigated are:

- Sex: Female and Male
- Number of failed previous treatments: ≤2 and >2

No hypothesis testing will be conducted in the subgroup analysis. Only the treatment differences relative to placebo and their associated 95% CIs will be estimated and displayed using a forest plot.

11.3.6 Exploratory Analysis of the Primary Endpoint

Two additional exploratory analyses using the alternative definitions of migraine day (1) based on daily symptoms and duration of the headache and (2) considering a mixture of headache day and migraine day in Section 3.6.1 to count and derive the MMDs will be conducted to evaluate the relevance of the different derivation strategies. The same MMRM model as that described for the primary analysis will be used to compare between EPTI and PBO averaged across Weeks 1-4.

11.4 Analysis Methodology for the Key Secondary Endpoints

11.4.1 Key Secondary Estimands

For continuous key secondary endpoints, estimands follow the same rationale and strategies as for the primary endpoint to address intercurrent events, see Section 11.3.1.

A summary of the binary key secondary estimand including intercurrent events and strategies can be found below in Table 3.

Table 3 Binary Key Secondary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Key Secondary Objectives	To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH	
Estimand Label	**Estimand 2a (Key Secondary)**	**Estimand 2b (Key Secondary)**
Estimand Description	Odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between EPTI and PBO regardless of the use of preventive migraine medication and interruptions/terminations of infusions, assuming other anti-CGRP treatment is not available.	
Target Population	Participants who suffer from migraine and MOH and who fulfil the inclusion and exclusion criteria.	
Treatment Conditions	Trial arm: BI and eptinezumab 100 mg Control arm: BI and placebo	
Endpoint	Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4)	Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12)
Population Level Summary	Odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-4	Odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo across Weeks 1-12
ICEs and Strategies		
ICE1 (new preventive medication)	Treatment policy	
ICE2 (anti-CGRP medication)	Hypothetical	
ICE3 (interruption/termination of infusion)	Treatment policy	
Rationale	A treatment policy strategy is used to estimate the treatment effect irrespective of new preventive migraine medication other than anti-CGRP treatment initiation and interruption/termination of infusions during trial period to reflect clinical practice. Under the assumption of less use of preventive migraine treatment in	

Key Secondary Objectives	To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH	
Estimand Label	**Estimand 2a (Key Secondary)**	**Estimand 2b (Key Secondary)**
	the eptinezumab group compared to the placebo group, this is considered to be a conservative approach. A hypothetical strategy is used to handle use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication. This will better reflect clinical practice, since it is not standard practice to prescribe two different anti-CGRP treatments simultaneously.	

Table 4 Key Secondary Endpoints and Analyses

Key Secondary Endpoint	Population Level Summary	Primary Analysis	Sensitivity Analysis
Change from baseline in the number of MMDs (Weeks 1-12) Change from baseline in number of MHDs (Weeks 1-4) Change from baseline in MHDs (Weeks 1-12)	The mean difference in the change of number of MMDs or MHDs from baseline between participants on eptinezumab and placebo	MMRM	pMI + MMRM
Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4) Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12)	Odds ratio of participants not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH between participants on eptinezumab and placebo	Logistic Regression	-
Change from baseline in average Daily Pain assessment score (Week 1-2)	The mean difference in the change from baseline in average Daily Pain assessment score between participants on eptinezumab and placebo	ANCOVA	ANCOVA on the days without taking any acute migraine medications
Change from baseline in monthly days with acute migraine medication use (Weeks 1-4) Change from baseline in monthly days with acute migraine medication use (Weeks 1-12)	The mean difference in the change from baseline in acute migraine medication use between participants on eptinezumab and placebo	MMRM	pMI + MMRM

11.4.2 Analysis of the Key Secondary Endpoints

The key secondary endpoints analysis will follow the testing strategy described in Section 11.2.

Change from baseline in MMDs (Weeks 1-12)

The endpoint will be analysed using the same MMRM model as that described for the primary analysis, except that the test will be based on the estimated mean MMDs, which is averaged over Weeks 1 to 4 (Month 1), Weeks 5 to 8 (Month 2), and Weeks 9 to 12 (Month 3). The estimates will be presented with p-values and 95% CIs.

The change from baseline in MMDs (Weeks 1-12) will be estimated as the average across the 3 4-week intervals, and the treatment effect will be calculated from the least squares estimates from the MMRM model for the month*treatment interaction via a contrast: (1/3, 1/3, 1/3, -1/3, -1/3, -1/3) comparing the effect of EPTI to the effect of PBO across Weeks 1-12.

Change from baseline in MHDs (Weeks 1-4)

Change from baseline in MHDs (Weeks 1-12)

The week 4 endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test be based on the number of MHDs. The baseline MMDs will be replaced with baseline MHDs. The estimates will be presented with p-values and 95% CIs.

For the Weeks 1-4 endpoint, the comparison will be the contrast between EPTI and PBO averaged across Weeks 1-4. For the Weeks 1-12 endpoint, the estimated mean difference in change from baseline in MHDs on EPTI and PBO will be averaged over Weeks 1 to 4 (Month 1), Weeks 5 to 8 (Month 2), and Weeks 9 to 12 (Month 3).

Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4)

Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-12)

The ICHD-3 diagnostic criteria for CM and/or MOH will be checked at Baseline, Week 4, Week 8, and Week 12 according to the IHS ICHD-3 criteria in the Section 3.9 and the endpoints, including the Weeks 1-12 endpoint, will be derived based on the description in the Section 15.1.6. Missing data after pro-rating will not be used in the analysis. Same manner will be applied to the derivation of Weeks 13-24 endpoint in Open-label Period. The treatment effect of these two endpoints will be analysed using logistic regression with baseline MMDs as a covariate, and treatment group, country and previous treatment failures (≤2, >2) as categorical variables based on the eDiary data collected over Weeks 1-4 and over Weeks 1-12 separately. The logistic regression model will be fitted using the maximum likelihood (ML) method and the logit link function. The odds ratios for EPTI compared to PBO will be estimated from the model and presented with p-values based on the likelihood ratio test and 95% CIs based on the profile likelihood. In case of convergence, sparsity or separation issues, refer to Section 15.15 for pooling rule.

Change from baseline in average Daily Pain assessment score (Week 1-2)

Daily pain assessment data will be collected in the headache eDiary via the question "*What was the worst pain intensity of this headache today?*". The pain intensity assessment is collected on a 3-point scale: Mild (score = 1), Moderate (score = 2) and Severe (score = 3).

For each day, the daily pain assessment score will be derived by averaging the worst pain intensity over all headaches of that day. For days on which no headache takes place during the relevant period, the daily pain score will be given as a score of 0. The average daily pain score will be calculated using the daily pain assessments collected during Weeks 1-2. For data

handling details, see Section 15.1.7. Change from baseline in average Daily Pain will be analysed using an ANCOVA with the average Daily Pain at baseline as a covariate and including treatment group, country, and previous treatment failures, as categorical variables. The estimates will be presented with p-values and 95% CIs.

Change from baseline in monthly days with acute migraine medication use (Weeks 1-4)
Change from baseline in monthly days with acute migraine medication use (Weeks 1-12)
The week 4 endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on monthly days with acute migraine medication use. The baseline MMDs will be replaced with monthly acute migraine medication use at baseline. The estimates will be presented with p-values and 95% CIs. For the week 12 endpoint, the estimated mean difference of monthly days with acute migraine medication uses on eptinezumab and placebo will be averaged over Weeks 1 to 4 (Month 1), Weeks 5 to 8 (Month 2), and Weeks 9 to 12 (Month 3). All medication collected in the eDiary as acute migraine medication regardless of whether they are taken to stop headache/migraine attacks will be accounted for in the analysis.

11.4.3 Rationale for Selected Analysis Method for the Key Secondary Endpoints

The rationale for the selected analysis method for change from baseline in monthly days with use of acute migraine medication (Weeks 1-4, Weeks 1-12) and change from baseline in MHDs (Weeks 1-4, Weeks 1-12) is covered by Section 11.3.3.

The logistic regression model has been chosen for all the binary key secondary endpoints due to its ability to provide estimates of treatment effects, adjusting for the effects of strata and covariates. Covariates are included in the model based on an approach including key factors representing trial design features/strata (stratum and treatment group), and baseline MMDs to account for its predictive ability for the response.

To compare the equality of two treatment effects in daily pain assessment score for Weeks 1-2, ANCOVA has been chosen to incorporate the covariate information of the analysis for one timepoint comparison.

11.4.4 Sensitivity Analysis of the Key Secondary Endpoints

For the key secondary endpoints change from Baseline in MMDs (Weeks 1-12), change from baseline in MHDs (Weeks 1-4, Weeks 1-12), and change from baseline in monthly days with use of acute migraine medication (Weeks 1-12), pMI will be conducted similarly to the first sensitivity analysis described for the primary endpoint, see Section 11.3.4.

For the change from baseline in average Daily Pain Assessment (Weeks 1-2), the sensitivity analysis will be conducted using the same ANCOVA model in Section 11.4.2 but we will derive the average daily pain assessment score on the days without taking any acute migraine medications. For data handling details, see Section 15.1.7.

11.4.5 Exploratory Analysis of the Key Secondary Endpoints

- Change from baseline in the number of MMDs using the alternative definitions of migraine day (Weeks 1-12)

- Change from baseline in the number of MHDs using the alternative definitions of migraine day (Weeks 1-4, Weeks 1-12)
- Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 1-4, Weeks 1-12)

Two additional exploratory analyses using the alternative definitions of migraine day (1) based on daily symptoms and duration of the headache and (2) considering a mixture of headache day and migraine day in Section 3.6.1 to count and derive the MMDs/MHDs will be conducted to evaluate the relevance of the different derivation strategies. The same models will be applied as those used for the primary definition of a migraine/headache day.

11.5 Analysis of Secondary Endpoints

For the Placebo-controlled Period, the secondary endpoints will be summarized by treatment group based on the FAS. For the Open-label Period, the secondary endpoints will be summarized by treatment sequence based on the APTS-OL.

For analyses related to eDiary, estimands follow the same rationale and strategies to address intercurrent events in Section 11.3.1 for continuous endpoints or Section 11.3.1. for binary endpoints in Placebo-controlled Period.

- Migraine on the day after dosing (Day 1) will be derived according to the descriptions in Section 15.1.3 and will be analysed using an extended Cochran-Mantel-Haenszel (CMH) test, adjusting for country and previous treatment failures (≤2, >2). The estimated proportions for EPTI and PBO will be presented.

The following binary endpoints for the Placebo-controlled Period will be analysed using logistic regression test including country and previous treatment failures as stratification variables (where the stratification variables will indicate the strata used for randomisation), similar to the one used in key secondary analysis in the not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH endpoint.

- Not fulfilling the ICHD-3 diagnostic criteria for CM (Weeks 1-4, Weeks 1-12)
- Not fulfilling the ICHD-3 diagnostic criteria for MOH (Weeks 1-4, Weeks 1-12)
- Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Weeks 13-24) (Only descriptive summaries)

The following continuous endpoints for the Placebo-controlled Period will be analysed using an MMRM model similar to the one used for primary analysis and key secondary analysis, the baseline MMD score will be replaced with the baseline score for the corresponding endpoint in the model.

- Change from baseline in MMDs with use of acute migraine medication (Weeks 1-12)
- Change from baseline in monthly days with triptan or ergotamine medication use (Weeks 1-12)
- Change from baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 1-12)
- Change from baseline in monthly days with combination non-opioid analgesics medication use (Weeks 1-12)

- Change from baseline in rate of migraines with severe pain intensity (Weeks 1-4, Weeks 1-12)
- Change from baseline in rate of headaches with severe pain intensity (Weeks 1-4, Week 1-12)
- Change from baseline to Weeks 13-24 in MMDs (Only descriptive summaries)
- Change from baseline to Weeks 13-24 in MHDs (Only descriptive summaries)
- Change from baseline to Weeks 13-24 in monthly days with acute migraine medication use (Only descriptive summaries)
- Change from baseline to Weeks 13-24 in monthly days with triptan or ergotamine medication use (Only descriptive summaries)
- Change from baseline to Weeks 13-24 in monthly days with individual non-opioid analgesics or NSAID medication use (Only descriptive summaries)

For the following endpoints based on response rates, treatment effects of EPTI compared to PBO will be analysed using logistic regression. The model will include baseline MMDs or MHDs as a continuous covariate, and treatment, country and previous treatment failures as factors. The logistic regression model will be fitted using the maximum likelihood (ML) method and the logit link function. For handling of missing MMD and MHD values, see Section 15.1.2. The odds ratios for EPTI compared to PBO will be estimated from the model and presented with p-values based on the likelihood ratio test and 95% CIs based on the profile likelihood. In case of convergence, sparsity or separation issues, refer to Section 15.15 for the pooling rule.

- Response: ≥50% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12)
- Response: ≥75% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12)
- Response: ≥50% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12)
- Response: ≥75% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12)

The following endpoints based on health-related quality of life scores test between EPTI and PBO at Week 4, Week 12 will use the similar MMRM model defined in the primary analysis. The baseline MMD score will be replaced with the baseline score for the corresponding endpoint in the model:

- Change from baseline to Week 4 and Week 12 in the HIT-6 total score
- Change from baseline to Week 4 and Week 12 in the mMIDAS total score
- Change from baseline to Week 4 and Week 12 in the MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function)
- Change from baseline to Week 4 and Week 12 in the EQ-5D-5L VAS score
- Change from baseline to Week 12 in the WPAI:M sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment)
- Change from baseline to Week 4 and Week 12 in HADS – depression, and anxiety subscale scores

- TSQM-9 score at Week 4 and Week 12 (Effectiveness, Convenience, Overall Satisfaction) (exclude baseline covariate in the model)
- PGIC score at Week 4 and Week 12 (exclude baseline covariate in the model)

The endpoint based on MBS scores test between EPTI and PBO at Week12 will use similar ANCOVA model defined in the analysis of key secondary endpoint: change from baseline in average Daily Pain assessment score.

- MBS score at Week 12 (exclude baseline covariate in the model)

The following endpoints based on diary data and health-related quality of life scores between EPTI-EPTI and PBO-EPTI will be summarized by descriptive tables.

- Change from baseline to Week 24 in average Daily Pain assessment score
- Change from baseline to Week 24 in the HIT-6 total score
- Change form baseline to Week 24 in the mMIDAS total score
- Change from baseline to Week 24 in the MSQ v2.1 sub-scores
- Change from baseline to Week 24 in the EQ-5D-5L VAS score
- Change from baseline to Week 24 in the WPAI:M sub-scores
- Change from baseline to Week 24 in HADS sub-scores
- TSQM-9 sub-scores at Week 24
- PGIC score at Week 24
- MBS score at Week 24

Descriptive tables displaying the distribution of answers to the items in HCRU at each visit will be provided by treatment group.

11.6 Analysis of Exploratory Endpoints

Analysis of exploratory endpoints for primary efficacy objectives will be based on FAS. For the Open-label Period, the exploratory endpoints will be summarized by treatment sequence based on the APTS-OL.

For analyses related to eDiary, estimands follow the same rationale and strategies to address intercurrent events in Section 11.3.1 for continuous endpoints or Section 11.4.1. for binary endpoints in Placebo-controlled Period.

- Complete withdrawal of acute headache medication (Weeks 1-4, Weeks 5-8, Weeks 9-12)

Participants completely withdrawn of acute headache medication is defined as the participants doesn't take any acute migraine medication during the 4-week interval period of interest. Complete withdrawal of acute headache medication will be analysed using logistic regression including country and previous treatment failures as stratification variables (where the stratification variables will indicate the strata used for randomisation), similar to the one used in key secondary analysis in the not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH endpoint.

To investigate the efficacy of eptinezumab as add-on to BI on level of daily physical activity and sleep using a wearable digital device (subset), the following continuous endpoints will be summarized:

- Change from baseline to Week 1-4 and Week 1-12 of passive registration of movement (actigraphy) (average per 28 days)
  - Number of average total minutes in no motion (0 - <10 a.U.)
  - Number of average total minutes with light motion (10 - <50 a.U.)
  - Number of average total minutes with moderate motion (50 - <100 a.U.)
  - Number of average total minutes with vigorous motion (≥ 100 a.U.)
- Change form baseline to Week 1-4 and Week 1-12 in sleep metrics assessment as assessed by actigraphy (average per 28 days)
  - Number of average total minutes of Total Sleep Time
  - Average proportion of Effective Sleep
  - Number of average total minutes of Wake After Sleep Onset
  - Number of average total minutes of Sleep Onset Latency

All analyses will also be done by week, for example change from baseline to Week 1, baseline to Week 2, and until baseline to Week 12.

To investigate the efficacy of eptinezumab as add-on to BI on level of analgesic dependence, change from baseline to Week 12 in SDS:H score will be analysed using an ANCOVA model similar to the one used for key secondary analysis.

- Change from baseline to Week 12 in SDS:H score

The number of days with auras without headache is derived based on the information in the aura without headache eDiary. The endpoint will be analysed in the subgroup of FAS participants which are diagnosed as migraine participants with aura at baseline as per the doctor's diagnosis in the eCRF. The change from baseline in number of days with auras without headache for the Placebo-controlled Period will be analysed using an MMRM model similar to the one used for primary analysis and key secondary analysis, the baseline MMD score will be replaced with the baseline number of days with auras without headache in the model.

- Change from baseline in number of days with auras without headache (Weeks 1-4, Weeks 1-12, Weeks 13-24) (Only descriptive summaries for Weeks 13-24)

The change from baseline in duration of severe pain continuous endpoint for the Placebo-controlled Period will be analysed using an MMRM model similar to the one used for primary analysis and key secondary analysis, the baseline MMD score will be replaced with the baseline duration of severe pain in the model.

- Change from baseline in duration of severe pain (Weeks 1-4, Weeks 1-12, Weeks 13-24) (Only descriptive summaries for Weeks 13-24)

The duration of severe pain is derived based on the collected information in the headache eDiary via the question "*What was the worst pain intensity of this headache today?*". For the relevant time period, for all headaches during that period, the duration of severe pain should be summed up over all days on which severe pain ever occurred. If more than 14 days are reported eDiary days, then the number of days with severe pain are calculated based on these days and this

number is prorated. If less than 14 days are reported eDiary days, then the number of days with severe pain will be set to missing.

12 Safety

12.1 Adverse Events

12.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, graphs, and listings will be based on the APTS for the Placebo-controlled Period and the APTS-OL for the Open-label Period.

All the tables and graphs will be presented by treatment group for the Placebo-controlled Period and by treatment sequence group for the Open-label Period, unless otherwise specified.

Tables by preferred term and tables by SOC and preferred term will be sorted in descending order based on the percentages of participants with these adverse events in EPTI-EPTI or PBO-EPTI group.

Unless otherwise specified, the summaries of adverse events will include the number and percentage of participants with an adverse event. In tables displaying SOC or preferred terms, participants are counted only once within each SOC or preferred term.

Listings of adverse events will be sorted by treatment group including participant ID with site ID, Age, Sex, Race, AE number, SOC/PT/investigator term, AE start date/time, AE stop date/time/ongoing, date of first IMP infusion, date of the latest IMP infusion prior to the adverse event, time since latest IMP infusion, duration of the adverse event, frequency type (continuous/Intermittent), intensity, seriousness, relationship to IMP (Probable/Possible/Not Related: Specify), action taken with IMP and outcome. For adverse events that change in intensity, each intensity will be included. In listings of adverse events, start or stop dates will be displayed as collected also in case of partially or completely missing dates.

All adverse events will be coded using MedDRA, Version 25.0 or later.

12.1.2 Classification of Adverse Events

Adverse events will be classified according to the time of onset of the adverse event:

pre-treatment adverse event – an adverse event that starts on or after the date the participant signed the *Informed Consent Form* and prior to the date and time of first dose of IMP

treatment-emergent adverse event (TEAE) – an adverse event that starts during or after administration of the first dose of IMP, or a pre-treatment adverse event that increases in intensity or becomes serious during or after administration of the first dose of IMP

For handling of adverse events with incomplete start dates to facilitate this classification, see Section 15.14.3. Note that adverse events with incomplete start dates will be classified as treatment-emergent simply if the imputed start date is on or after the date of first IMP infusion, since the start time of the adverse event will not be imputed, unless the investigator in such a case has assessed that the causality to IMP is “Not Related - Prior to IMP”.

An adverse event is considered causally related to the use of the IMP when the causality assessment by the investigator is probable or possible. If the causality assessment is missing, the adverse event is considered causally related.

12.1.3 Allocation of TEAEs to Treatment Periods

TEAEs will be allocated to treatment periods according to the time of onset of the adverse event:

- *TEAE in the Placebo-controlled Period* – a TEAE that starts before the date and time of the start of Visit 5 IMP infusion, or, for the participants with no Visit 5 IMP infusion, a TEAE that starts before Week 12.
- *TEAE in the Open-label Period* – a TEAE that starts, increases in intensity or becomes serious during or after administration of Visit 5 IMP infusion.

This implies that for participants in the APTS-FU, adverse events reported after withdrawal in the Placebo-controlled Period but before Week 12, will be allocated to the Placebo-controlled Period.

For allocation of TEAEs to treatment periods, the same rule for imputed dates as specified in Section 15.14.3 applies, i.e. for incomplete start dates, only the imputed start date and not the time (which will not be imputed) of the adverse event will be taken into account in the allocation of the TEAE to periods.

If an adverse event starts on the day of the Visit 5 IMP infusion, but with an unknown start time, the adverse event will be classified as treatment-emergent in the Placebo-controlled Period.

12.1.4 Overview of Adverse Events

For the APTS and APTS-OL, respectively, an overview of the numbers and percentages of participants with TEAEs, TEAEs related to IMP, serious adverse events (SAE)s, TEAE intensity (Mild, Moderate, Severe), TEAEs leading to infusion interruption, TEAEs leading to withdrawal from treatment, and TEAEs in participants who died will be provided. For the APTS-FU, an overview of the numbers of participants with TEAEs, TEAEs related to IMP, SAEs, and TEAEs in participants who died will be provided. For TEAEs, TEAEs related to IMP, and SAEs, the total number of events will be provided.

A listing of all adverse events occurring before entering the Open-label Period, including a flag for TEAEs will be provided based on APRS. For participants in the APTS-FU set, adverse events reported after withdrawal in the Placebo-controlled Period but before Week 12, will be included in this list.

A listing of all adverse events starting at or after entering the Open-label Period, including a flag for TEAEs will be provided based on the APTS-OL.

For participants who do not enter the Open-label Period, for example study withdrawals during the Placebo-controlled Period, a separate listing of TEAEs with start date after Week 12 will be provided based on the APTS-FU.

12.1.5 Treatment-emergent Adverse Events

The following summaries will be provided by treatment group for the Placebo-controlled Period and by treatment sequence for the Open-label Period:

- TEAEs by SOC and preferred term
- TEAEs with an incidence ≥2% in any treatment group by preferred term
- causally related TEAEs by SOC and preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*), SOC, and preferred term
- causally related TEAEs by intensity, SOC, and preferred term
- TEAEs occurring on the day of dosing after infusion start by SOC and preferred term (this includes day of Visit 2 infusion for the Placebo-controlled Period and day of Visit 5 infusion for the Open-label Period)

The summaries will be provided for the APTS for the Placebo-controlled Period and for APTS-OL for the Open-label Period.

12.1.6 Serious Adverse Events

Treatment-emergent SAEs will be summarized by treatment group for the Placebo-controlled Period based on APTS and by treatment sequence for the Open-label Period based on APTS-OL by:

- SOC and preferred term

All SAEs occurring before entering the Open-label Period will be listed for the APRS.

All SAEs occurring at or after entering the Open-label Period will be listed for the APTS-OL.

12.1.7 Adverse Events Leading to Withdrawal from Treatment

TEAEs leading to withdrawal will be summarized for by treatment group the Placebo-controlled Period based on APTS and by treatment sequence for the Open-label Period based on APTS-OL by:

- SOC and preferred term

All AEs leading to withdrawal before entering the Open-label Period will be listed for the APRS.

All AEs leading to withdrawal occurring at or after entering the Open-label Period will be listed for the APTS-OL.

12.1.8 Adverse Events Leading to Trial Drug Infusion Interruption

All AEs leading to trial drug infusion interruption before entering the Open-label Period will be listed for the APRS.

All AEs leading to trial drug infusion interruption occurring at or after entering the Open-label Period will be listed for the APTS-OL.

TEAEs leading to trial drug infusion interruption will be summarized for the Placebo-controlled Period based on APTS and for the Open-label Period based on APTS-OL by:

- SOC and preferred term

12.1.9 Deaths

All the adverse events in participants who died before entering the Open-label Period will be listed for the APRS.

All the adverse events in participants who died after entering the Open-label Period will be listed for the APTS-OL.

12.1.10 Adverse Events of Special Interest

Treatment-emergent adverse events of special interest (AESI) will consist of the preferred terms defined by the SMQs/HLTs/HLGTs listed in Table 15 .

The following summaries of treatment-emergent AESIs will be provided by treatment group for the Placebo-controlled Period based on the APTS and by treatment sequence for the Open-label Period based on the APTS-OL:

- AESIs by SOC and preferred term
- AESIs by SOC and preferred term, separately for each individual event category

All AESIs occurring before entering the Open-label Period will be listed for the APRS.

All AESIs occurring at or after entering the Open-label Period will be listed for the APTS-OL.

The listings will be repeated for all AEs belonging to the Hypersensitivity and Anaphylactic Reactions event category only, see Table 15.

12.2 General Methodology for Other Safety Data

Unless otherwise specified, tables, graphs, and listings will be based on the APTS for the Placebo-controlled Period and APTS-OL for the Open-label Period.

All tables and graphs will be presented by treatment group for the Placebo-controlled Period and by treatment sequence group for the Open-label Period.

The denominators for the summaries of a given variable will be based on the number of participants with non-missing values at a given visit or during the assessment period.

Descriptive statistics for the safety variables, both absolute values and changes from baseline, will be presented by visit, separately for each period.

12.3 Vital Sign Measurements

Vital signs including blood pressure, pulse, respiratory rate, and temperate will be summarized based on APTS in Placebo-controlled Period and APTS-OL in Open-label Period by position, visit and treatment group.

Summary of participants with potentially clinically significant vital sign results will also be summarized using the PCS criteria in Appendix 17.2. The number and percentage of participants with at least one potentially clinically significant (PCS) value at any post-baseline assessment time point will be summarized by vital signs, separately for each period. All available assessments in each period will be included in the evaluation of PCS values.

For participants with post-baseline PCS values in the Placebo-controlled Period, listings will be provided including all the values for those participants for the variable prior to entering the

Open-label Period, with flagging of PCS values and out-of-reference-range values. For participants with PCS values occurring after start of Visit 5 IMP infusion, similar listings will be provided including all the values for those participants for the variable. For participants in the APTS-FU set, i.e. for the participants who do not enter the Open-label Period, for example study withdrawals during the Placebo-controlled Period, with PCS values occurring after Week 12, similar listings will be provided including all the values for those participants for the variable.

12.4 Other Safety Endpoints

12.4.1 Screening Assessments

Clinical laboratory, ECG, reproductive system, physical and neurological examinations are performed at screening. Any abnormal finding or out-of-range value considered clinically significant by the investigator will be recorded as an adverse event on an *Adverse Event* Form.

The Columbia-Suicide Severity Rating Scale (C-SSRS)[3] is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of participants participating in a clinical trial. The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of ideation, and 4 questions addressing suicidal behaviour. For this trial, the following versions of the scale are used: the "Baseline/Screening" version (lifetime and 1 year assessment).

Table 5 C-SSRS Scores

C-SSRS Score		Related to:
1	Wish to be dead	Suicidal ideation
2	Non-specific active suicidal thoughts	
3	Active suicidal ideation with any methods (not plan) without intent to act	
4	Active suicidal ideation with some intent to act, without specific plan	
5	Active suicidal ideation with specific plan and intent	
6	Preparatory acts or behaviour	Suicidal behaviour
7	Aborted attempt	
8	Interrupted attempt	
9	Non-fatal suicide attempt	
10	Completed suicide (only applicable for the post-baseline assessments)	

13 Interim Analysis

No interim analysis is planned.

14 Sample Size Considerations

The sample size calculation assumes that the treatment effect of eptinezumab 100 mg compared to placebo in change from baseline in MMDs (Weeks 1 to 4) will be -1.5 MMDs. The difference between eptinezumab 100 mg and placebo was -2.0 in Study 011, a trial that did not include education on MOH, after 4 weeks and -3.1 in the subgroup of participants with CM and MOH. The difference between withdrawal from treatment with and without preventive treatment was -1.7 and -1.4 days after 2 and 4 months. The SD is assumed to be 6.2, based on the averaged SD

across treatment groups in the MOH subgroup of Study 011 on the change from baseline in MMDs (Weeks 1 to 4).

Based on the assumed effect size and SD, using a two-sided test on the 5% significance level, 270 participants per treatment group will provide 80% power for showing an effect on the primary endpoint. Assuming that 5% of participants will not contribute data to the analysis. 285 participants randomized per treatment group, or 570 participants randomized in total will be needed.

A sample size re-assessment will be conducted on blinded data when approximately 70% of the participants have been randomized. The SD is estimated in the same model as for the primary endpoint, except that all terms including treatment (main effect of treatment group and interaction between treatment group and month) are excluded. Based on this estimate, the sample size may be increased.

15 Details on Data Handling

15.1 eDiary

15.1.1 Monthly Migraine Days /Monthly Headache Days

The following describes the derivation of MMDs. The derivation of MHDs follows the same principles. Definitions of a migraine day and a headache day are described in Section 3.6.

Pooling of symptoms

To assess whether a headache is a migraine headache, daily reported symptoms will be pooled to assess the migraine criteria described in Section 3.6. The worst reported symptom will be used, for example, if different levels of worst pain have been reported on different days of the same headache, the worst of these levels will be used to assess the migraine criteria.

Regarding successful medication use for the criterion “a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication”: a medication can only be considered successful if the question “*Did at least one of the medications you took today successfully treat your headache?*” is answered positively on the same day as the medication intake date.

4-Week Intervals

For Baseline and each 4-week period post-baseline in the trial, the number of MMDs will be derived as the number of migraine days within each 28-day interval using the imputation rules described below. The 4-week periods post-baseline that are considered are the following: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20 and Weeks 21-24.

In general, for 4-week periods where the number of reported eDiary days are at least 14 days out of the 28 days, prorating will be used to calculate the MMDs, and for 4-week periods where the number of reported eDiary days are less than 14 days out of the 28 days, the MMDs will be set to missing. Once prorating has been applied, a non-missing 4-week MMD value is considered a valid assessment.

Prorating

Intended to be used for 4-week periods where the eDiary is completed on at least 14 out of the 28 days, the prorating procedure consists of imputing days with missing information with the observed mean number of migraine days in the period as follows:

28*(*Reported Migraine Days/Reported eDiary Days*)

This imputation rule will also be used for the Baseline value regardless of the number of reported eDiary days in the screening period.

When the number of MMDs have been calculated for a given 4-week period, the result will be rounded to two decimals.

15.1.2 Migraine/Headache Responder Rates

The following describes the derivation for migraine responder rates. The derivation for headache responder rates is similar.

The following responder rates will be derived: 50% and 75%. A responder is a participant, who achieves a ≥50% reduction or ≥75% reduction, respectively, compared to the baseline number of MMDs. The derivation of these responder endpoints will be based on the number of MMDs resulting from the imputations described in the Section 15.1.1.

For each 4-week period post-baseline in the trial, the responder status of a participant will be derived based on the percentage change from baseline in MMDs. If the MMDs value is missing for the month in question, the response status will also be missing.

For Weeks 1-4, the 50% and 75% responder status will be derived as follows, using 50% response as an example:

$$50\%\ \text{Responder Status}(\text{Weeks } 1-4) = \begin{cases} 1, \text{if } \dfrac{(\Delta_{M1})}{Baseline} \leq -0.5 \\ 0, \text{if } \dfrac{(\Delta_{M1})}{Baseline} > -0.5, \end{cases}$$

For Weeks 1-12, the 50% and 75% responder status will be derived as follows, using 50% response as an example:

$$50\%\ \text{Responder Status}(\text{Weeks } 1-12) = \begin{cases} 1, \text{if } \dfrac{\text{ave}(\Delta_{M1}, \Delta_{M2}, \Delta_{M3})}{Baseline} \leq -0.5 \\ 0, \text{if } \dfrac{\text{ave}(\Delta_{M1}, \Delta_{M2}, \Delta_{M3})}{Baseline} > -0.5, \end{cases}$$

where Δ_{Mi} is the change from baseline value for month *i*. For 12-week intervals, if any of the months included in the calculation have a missing value of MMDs after prorating, the responder status will be derived based on the available values.

15.1.3 Percentage of Participants with Migraines on the Day After Dosing (Day 1)

The percentage of participants with a migraine on the day after dosing will be derived based on whether the participant filled out the eDiary on Day 1 or not. If the participant filled out the eDiary on Day 1, the participant will have a rate of either 0 or 100 on Day 1 that is 0 if the

participant experienced no migraine on Day 1 and 100 if the participant did experience a migraine on Day 1.

If the participant did not fill out the eDiary on Day 1, the rate for the participant will be imputed as:

100 * (*Number of MMDs Weeks 1-4*/28),

where the number of MMDs for Weeks 1-4 is derived as described in Section 15.1.1. Note that if the number of MMDs for Weeks 1-4 is missing for the participant and the participant did not fill out the eDiary on Day 1, the Day 1 rate will be missing.

15.1.4 Migraines/Headaches with Severe Pain Intensity and Migraine Attacks/Headache Episodes

The percentage of migraines/headaches with severe pain intensity is derived based on the derived number of monthly migraine attacks and headache episodes.

Migraine attack and headache episodes are defined in the Section 3.8. Headache severity is collected on a 3-point scale, Mild, Moderate and Severe. Migraines and headaches with severe pain intensity on at least one day are defined as migraine attacks/headache episodes with a reported severity of "Severe".

The following describes the derivation of number of monthly migraine attacks. The derivation of monthly headache episodes follows the same principles.

The derivation of the number of monthly migraine attacks will follow the imputation rules described in Section 15.1.1 for MMDs, replacing *Reported Migraine Days* with *Reported Migraine Attacks* everywhere. As an example, the number of monthly migraine attacks for a participant with 14 days or more of eDiary reporting in a 4-week period will be derived as:

28 * (*Reported Migraine Attacks/Reported eDiary Days*)

The number of monthly migraines with severe pain intensity is derived in the same way using only migraine attacks with a reported severity of "Severe".

The percentage of migraines and headaches with severe pain intensity is then calculated as the percentage of migraine attacks/headache episodes with severe pain intensity out of the number of migraine attacks/headache episodes. Participants with no migraine attacks/headache episodes are included with a rate of 0.

15.1.5 Monthly Days with Acute Migraine Medication Usage and MMDs with Acute Migraine Medication Usage

In the aura without headache and headache diaries, as well as the evening diary, participants are asked each day to fill out whether they used any of the following medications during that day: ergotamine, triptan, non-opioid analgesic, barbiturates, opioid, or combination analgesic. A day where the participant answers that they took any of those in the diary is considered a day with use of acute migraine medication.

The number of days with acute migraine medication usage is then derived for each 4-week period using the imputations described in Section 15.1.1 and replacing *Reported Migraine Days* with *Reported Acute Migraine Medication Days* everywhere as well as replacing *Reported eDiary Days* with *Reported Medication Days*, where a "*Reported Medication Day*" is defined as

a Reported eDiary Day where at least one of the following pieces of information are available:

- A response in the Headache eDiary question "Did you take any medications to treat this headache today?"
- A response in the Evening eDiary question "Did you take any medication to prevent a headache today?"
- A response in the Aura without Headache eDiary question "Did you take any headache medication related to this aura today?"

A missing Medication Day is defined as a day that is not a Reported Medication Day.

If a reported acute migraine medication span across two 4-week periods, then it will be counted in both periods according to the medication start date/preceding period end date and subsequent period start date/medication end date.

The number of days with each available medication type taken will be derived in a similar manner as above.

Additionally, the MMDs with acute migraine medication usage will be derived. The number of MMDs with acute migraine medication is derived in a similar manner as above, except that only days that qualify as a migraine day will be considered.

15.1.6 Not fulfilling the ICHD-3 Diagnostic Criteria for CM/MOH

The ICHD-3 diagnostic criteria for CM is either 1, or 0 if the criteria are not fulfilled, or the criteria are fulfilled, respectively, based on the criteria in Section 3.9. Similar to the ICHD-3 diagnostic criteria for MOH, 1 if the criteria are not fulfilled and 0 if the criteria are fulfilled.

For Weeks 1-4 criteria testing, 28-days period eDiary data are used for derivations. If the CM criteria is not fulfilled, set to '*1*', otherwise set to '*0*'. Similar for the MOH criteria diagnosis. Similar procedure for the Weeks 5-8, and Weeks 9-12 criteria. For the "CM nor MOH" criteria, for each of the 4-week periods, a participant is classified as "not fulfilled" if both the CM and MOH criteria are not fulfilled, and as "fulfilled" if at least one of the CM or MOH criteria are fulfilled.

For Weeks 1-12 criteria testing, 3 x 28-days period eDiary data are used for derivations. If participant not fulfills the CM criteria in all three 28-days periods, set to '*1*', otherwise set to '*0*'. If any of the 28-days periods included in the calculation is missing after prorating, the status of CM will be derived based on the available values. Similar for the MOH criteria diagnosis. For the "CM nor MOH" criteria, a participant is set to '1' ("not fulfilled") if both these CM and MOH criteria are not fulfilled, and set to '0' ("fulfilled") if at least one of the CM or MOH criteria are fulfilled.

Note that the IHS ICHD-3 Guideline stated in Panel 3 (Section 3.6) can be interpreted as it would be enough to be free from CM during just one of the three 28-days periods to be defined as "not fulfilled". The Weeks 1-12 criteria testing used for this trial is thus more conservative than the IHS ICHD-3 Guideline stated in Panel 3.

15.1.7 Average Daily Pain Assessment Score

Average daily pain assessment score will be calculated based on days from a headache where at least one of the days of the headache had pain assessment reported for Week 1, Week 2, Weeks

1-2 and any given 4-week period, regardless of the number of reported eDiary days with the period. If a day is a reporting day with missing daily pain assessment and it is not a day on which no headache takes place, then this day will be imputed based on the average daily pain scores from the other day(s) of the same headache. Otherwise, it will be treated as a missing day.

For the sensitivity analysis, only reported eDiary days without taking any acute migraine medications will be included in the calculation of the average daily pain score in the respective period. If a day is a reporting day with missing daily pain assessment and it is not a day on which no headache takes place, then this day will be imputed based on the average daily pain scores from the other day(s) without taking any acute migraine medications of the same headache. Otherwise, it will be treated as a missing day. If the participant has no such days in the Week 1, Week 2, Weeks 1-2 period, or in any 4-week period, applying a conservative approach, the value will be set to 3 ("Severe") for that period.

15.2 Headache Impact Test (HIT-6)

The HIT-6 (v1.0)[4] is a Likert-type, self-reporting questionnaire designed to assess the impact of an occurring headache and its effect on the ability to function normally in daily life. The HIT-6 contains 6 questions, each item is rated from "never" to "always" with the following response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. The total score for the HIT-6 is the sum of each response score and ranges from 36 to 78. The life impact derived from the total score is described as followed: Severe (≥60), Substantial (56-59), Some (50-55), Little to None (≤49).

15.3 Migraine Disability Assessment, Modified Version (mMIDAS)

The mMIDAS[5] is a self-reporting questionnaire designed to assess absenteeism (complete disability) and presenteeism (reduced participation) in several domains, including work, school, family, social, and leisure activities. The total number of days with disability is rated on a 4-point scale, from the lower total score that indicates a Little or No Disability (0-5 days); Mild Disability (6-10 days); Moderate Disability (11-20 days) to the higher total score that indicates a Severe Disability (21 and more days). As the 20007A trial use the mMIDAS with a 1-month recall period, whereas the reference number of days provided in this paragraph is based on the original MIDAS version with a 3-months recall period, the disability levels in terms of number of days have to be adapted to a 1-month period. The following scoring will be used: Little or No Disability (0-1 days), Mild Disability (2-3 days), Moderate Disability (4-6 days) and Severe Disability (7 days or more). Both the mMIDAS scores and the mMIDAS scores multiplied by 3 will be presented.

15.4 Patient Global Impression of Change (PGIC)

The PGIC is a single patient-reported item reflecting the participant's impression of change in their disease status since the Baseline visit (that is, in relation to activity limitations, symptoms, emotions, and overall quality of life).

The item is rated on a 7-point scale, where a low score indicate improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse).

15.5 Most Bothersome Symptom (MBS)

The Investigator will verbally obtain the most bothersome symptom associated with the participant's migraines during the Screening Visit. Participants will be asked to rate the improvement in this symptom from screening on a 7-point scale identical to the scale used for the PGIC, i.e. the scale ranges from 1 (very much improved) to 7 (very much worse).

The MBS areas include: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, and other.

15.6 Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ v2.1)

The MSQ v2.1[6] is a participant-reported outcome designed to assess the quality of life in participants with migraine. It consists of 14 items covering three domains: role function restrictive (7 items); role function preventive (4 items); and emotional function (3 items). Each item is scored on a 6-point scale ranging from 1 (none of the time) to 6 (all of the time). Raw domain scores are summed and transformed to a 0 to 100 point scale. Higher scores indicate better quality of life.

The items going into each domain[7] are specified in Table 6.

Each item score is mapped from the recorded value of the item as shown in Table 7.[8]

For each domain, the score is derived from the final item values by summing the scores from items within each domain and transforming the summed scores as shown in Table 8.

Table 6 MSQ v.2.1 Domains

Domain	Item number	Abbreviated content
Role function restrictive	1	. . . . . interfered with how well you dealt with family, friends, and others
	2	. . . . . interfered with your leisure time activities such as reading or exercising
	3	. . . . . had difficulty in performing work or daily activities
	4	. . . . . kept you from getting as much done at work or at home
	5	. . . . . limited your ability to concentrate on work or daily activities
	6	. . . . . left you too tired to do work or daily activities
	7	. . . . . limited the number of days you felt energetic
Role function preventive	8	. . . . . cancelled work or daily activities . . .
	9	. . . . . needed help in handling routine tasks
	10	. . . . . stopped work or daily activities . . .
	11	. . . . . not able to go to social activities . . .
Emotional function	12	. . . . .felt fed up or frustrated
	13	. . . . . felt like a burden on others
	14	. . . . . afraid of letting others down

Table 7 MSQ v.2.1 Item Values

Response categories	Pre-coded item value	Final item value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Table 8 Derivation of MSQ v.2.1 Domain Scores

Domain	Sum of item scores range	Derivation
Role function restrictive	7 to 42	(Summed score – 7)*100/35
Role function preventive	4 to 24	(Summed score – 4)*100/20
Emotional function	3 to 18	(Summed score – 3)*100/15

15.7 Hospital Anxiety and Depression Scale (HADS)

The HADS is a patient-rated scale designed to assess psychological distress in non-psychiatric participants. The HADS consists of two sub-scales: The D-scale measures depression and the A-scale measures anxiety. Each sub-scale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each sub-scale ranges from 0 to 21 and are analysed separately.

15.8 Euroqol 5 Dimension – 5 Levels (EQ-5D-5L)

The EQ-5D-5L[9] is a patient-reported assessment designed to measure the participant's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated.

The VAS is scored separately and ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

15.9 Work Productivity and Activity Impairment: Migraine (WPAI:M)

The WPAI[10] is a patient self-rated scale designed to provide a quantitative measure of the work productivity and activity impairment due to a specific health problem (WPAI:M). The WPAI assesses activities over the preceding 7 days and consists of 6 items: 3 items assess the number of hours worked, the number of hours missed from work due to the participant's condition, or due to other reasons, and 2 visual numerical scales to assess how much the participant's condition affects their productivity at work and their ability to complete normal daily activities.

The derivation of the WPAI:M sub-scores[11] is given in Table 9, where Q1-Q6 refers to question 1-6 in the questionnaire. If both Q2 and Q4 has a score of 0 then both the Absenteeism and the Work productivity loss sub-scores are set to missing.

Table 9 Derivation of WPAI:M sub-scores

Sub-score	Description	Derivation
Absenteeism	Percent work time missed due to migraine	100*Q2/(Q2 + Q4)
Presenteeism	Percent impairment while working due to migraine	100*Q5/10
Work productivity loss	Percent overall work impairment due to migraine	$100 * \left(\frac{Q2}{Q2+Q4} + \left(1 - \frac{Q2}{Q2+Q4}\right) * \frac{Q5}{10}\right)$
Activity impairment	Percent activity impairment due to migraine	100*Q6/10

15.10 Treatment Satisfaction Questionnaire for Medicine – 9 Items (TSQM-9)

The TSQM-9[12] is a generic questionnaire assessing the participant's satisfaction with the medication. The tool consists of 9 items addressing effectiveness, convenience, and overall satisfaction of the IMP with 7-point scale for each item from 1- Extremely Dissatisfied to 7 - Extremely Satisfied. The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain. See Table 10 for derivation.

Table 10 Derivation of TSQM-9 Domain Scores

Domain	Derivation
Effectiveness score	[(Q1 + Q2 + Q3) – 3)]/18*100
Convenience score	[(Q9 + Q10 + Q11) – 3)]/18*100
Overall satisfaction score	[(Q12 + Q13 + Q14) – 3)]/14*100

15.11 Health Care Resource Utilization (HCRU)

Migraine-specific healthcare resource utilization information will be collected in terms of outpatient health care professional visits (number of visits to doctor/general practitioner and number of visits to a specialist), number of emergency room visits, number of hospital admissions, as well as number of overnight hospitals stays during the past 4 weeks.

The items from the questionnaire will be analysed separately.

15.12 Severity of Dependence Scale Adapted for Headache (SDS:H)

The SDS:H is a patient reported scale, designed to assess dependency-like behaviour in participants with headache. The SDS:H is performed as a semi-structured interview, where the following questions will be addressed: 1) Do you think your use of headache medication was out of control? 2) Did the prospect of missing a dose make you anxious or worried? 3) Did you worry about your use of your headache medication? 4) Did you wish you could stop? 5) How difficult would you find it to stop or go without your headache medication? Each item is scored on a 4-point scale ranging from 0 (never/almost never, question 1-4, and not difficult, question 5) to 3 (always/nearly always, question 1-4, and impossible, question 5).

15.13 Assigning Data to Visits

See Section 3.1 for definition of Baseline.

15.13.1 BI and SDS:H

With respect to the Brief Educational Intervention (BI), data will be assigned to visits, regardless of the timing of the BI, also in the case the BI was missed. If an observation for SDS:H exist with visit label equal to Visit 2, it will be assigned to Visit 2, also in the case it was done after the Visit 2 date. Similarly, if an observation for SDS:H exist with visit label equal to Visit 5, it will be assigned to Visit 5, also in the case it was done after the Visit 5 date.

15.13.2 Pharmacoeconomic Assessments (ePROs)

For treated patients withdrawing prior to Week 12, the withdrawal visit will also include efficacy evaluations (PGIC, MBS, HADS, HIT-6, mMIDAS, MSQ, EQ-5D-5L, HCRU, WPAI:M and TSQM-9). These assessments will be assigned to nominal Visit 5.

Using the same principle for participants withdrawing in the open-label period after infusion of the IMP at Visit 5, the ePRO assessments will be assigned to nominal Visit 7.

Unscheduled visits will not contain assessments of the ePROs mentioned above.

ePROs will be summarized based on the following visit assignment rules to be applied for each ePRO endpoint separately:

- If exactly one observation exists for a specific visit label, this should be used.
- If more than one observation exist for a specific visit label the following would apply:
    - Week 4 (Visit 3): Choose the observation closest to Analysis day (ADAY) = 26.
    - Week 12 (IMP Visit 5): If one or more observations exist that are made prior to the IMP infusion at visit 5, choose the one closest to the IMP infusion at visit 5. If no such observation exists, choose the one closest to ADAY = 82.
    - Week 24 (Visit 7): Choose the observation closest to 82 days after the IMP Visit 5 date.
- Any remaining observations that are not assigned to a visit after this procedure, will constitute candidates for assignment to a trial visit using the assignment rules for withdrawals stated above. In case there is any observation on Visit 5/Visit 7 reflecting a planned assessment, this will take precedence over the candidate. In case, no planned assessments are present at Visit 5 or Visit 7 visits, the observation closest to ADAY = 82, or 82 days after IMP Visit 5, respectively, will be chosen. For an observation to be assigned to Visit 7, IMP needs to have been administered at Visit 5.

15.13.3 Safety Variables

Vital signs

Vital signs will be assessed before and after infusion at nominal visits. For unscheduled or withdrawal visit assessments of vital signs, the values will be assigned a nominal visit according to Table 11 and Table 12.

Table 11 Visit Windows for Placebo-controlled Period – Vital Signs (Pulse rate, Blood Pressure, Temperature)

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Screening Visit)	-4	-28	Before day 0 and before first IMP infusion
V2 (Baseline Visit) pre-dose	0	0	Same day as first IMP infusion (Day 0) and prior to IMP infusion on that date
V2 (Baseline Visit) post-dose	0	0	After start of first IMP infusion to day 42
V5 pre-dose	12	84	Day 43 to start of V5 IMP infusion

Table 12 Visit Windows for Open-label Period – Vital Signs (Pulse rate, Blood Pressure, Temperature)

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Nominal Visit Day Relative to Visit 5 IMP Infusion	Time Window Relative to Visit 5 IMP Infusion
V5 post-dose	12	84	0	After start of V5 IMP infusion to day 42
V7	24	168	84	Day 43 to the day after the safety follow-up visit

If there is more than one assessment at a visit (either due to multiple assessments or because an unscheduled or withdrawal visit assessment is mapped to a nominal visit with an already existing value) the value that will be used in summary tables by visit will be the one closest to the nominal day for the visit but prioritizing values from scheduled visits above values from withdrawal or unscheduled visits. In the ordering of multiple values, assessments without recorded time will come after assessments with recorded time and the first in the ordering will be picked.

15.14 Missing Data Handling

15.14.1 Headache and Migraine Day

For the primary analysis a headache will be classified as a migraine or non-migraine headache based on available symptoms. If no symptoms are captured for a headache, i.e. no information on symptoms is available for any of the days of the headache, then each day of the headache will not be a reporting day, and it will be prorated.

For evaluations based on daily duration/symptoms for the exploratory analyses: days with missing information on symptoms will be imputed considering all days with information on symptoms available for that headache. If no symptoms are captured for the given day of the headache, then it will be considered a day with migraine, if either of the other days of the headache is a day with migraine; if no symptoms are captured for the given day of the headache,

and if all other days with symptoms are not days with migraine, then this day will also be a day without migraine; if no symptoms are captured for a headache, then each day of the headache will not be a reporting day, it will be prorated.

For participants diagnosed with migraine without aura, it will be assumed that on days for which the aura without headache eDiary is missing, no aura without headache took place.

15.14.2 Headache End Date and Time

If the end date and time for a headache recorded in the eDiary is missing, the headache end date and time will be imputed as follows:

• If there exists an entry in the evening eDiary at a date after the date of the start of the headache entered in the headache eDiary, the headache end date and time is imputed with the date and time of the last evening eDiary entry.

• If there are no entries in the evening eDiary after the date of the start of the headache entered in the headache eDiary, the headache end date and time is imputed with the start date of the headache and the time 23:59.

Note that for each participant, it is only possible to have a missing end date and time for the last headache ever entered, since a participant needs to complete a headache in order to report a new one in the headache eDiary.

15.14.3 Adverse Event Start and Stop Dates

Imputation of partially or completely missing dates will be included in data in order to document the classification of the treatment emergent status. For an adverse event with an imputed start date, the classification of treatment emergent will depend only on whether the imputed date is the same as the date(s) of infusion and not the timepoint of the infusion, since start times for adverse events will not be imputed. No duration will be calculated for adverse events with incomplete start-or-stop dates or for ongoing adverse events.

Imputation will follow the algorithm below. If an imputed start date after this procedure is after the end date, the start date will be set to the end date.

Start Dates

Participants with no IMP infusion

For participants who have not been treated, the imputation of AE start date will be performed as follows, where UK and UKN indicate unknown or missing day and month, respectively:

- UK-MMM-YYYY: The start date will be imputed with either the 1st of the month, or date of Visit 1. Date of Visit 1 will be used if that is the later of the two and if it is within the specified month and year
- UK-UKN-YYYY: The start date will be imputed with either JAN 1, or date of Visit 1. Date of Visit 1 will be used if it is within the specified year

If the AE start date is completely missing, it will be set equal to the date of Visit 1.

Patients who received IMP infusion

For participants, who have been treated, the imputation of AE start dates will be performed as follows:

- UK-MMM-YYYY:

  If the year and month are equal to the year and month of treatment start date, the adverse event start date is imputed with the date of IMP dose

  If the year is equal to the year of treatment start date: If the month is prior to the treatment start date, the adverse event start date is imputed with the last day of the month. If the month is equal to the month of the treatment start date, see above. If the month is after the month of the treatment start date, the adverse event start date is imputed with the first day of the month

  If the year is prior to treatment start date, the adverse event start date is imputed with the last day of the month

  If the year is after the year of treatment start date, the adverse event start date is imputed with the first day of the month
- UK-UKN-YYYY:
  - If the year is equal to the year of treatment start date, the adverse event start date is imputed with treatment start date
  - If the year is prior to the year of treatment start date, the adverse event start date is imputed with 31-DEC-YYYY
  - If the year is after the year of treatment start date, the adverse event start date is imputed with 01-JAN-YYYY

If the AE start date is completely missing, it will be set equal to treatment start date.

End Dates

Missing AE end dates will not be imputed.

Incomplete Intensity Change Dates

If the day is missing in a date of intensity change for an adverse event, the date will be imputed using the same algorithm as described above for incomplete adverse event start dates.
If this results in an imputed start date that is after the end date of the original event or after an intensity change that comes after the intensity change in question, the start date will be imputed with the end date of the original event or the date of the later intensity or change.

15.14.4 Medication Start and Stop Dates

Imputation of incomplete or partially missing dates will be performed in order to document the assigned categories specified in Section 8.

The algorithm for imputing the start dates will follow the one used for imputing adverse event start dates, see Section 15.14.3.

For imputing stop dates, the following will apply, where UK and UKN indicate unknown or missing day and month, respectively:

- UK-MMM-YYYY: Medication end date is imputed with the last day of the month

- UK-UKN-YYYY: Medication end date is imputed with 31-DEC-YYYY

Medications marked as ongoing are considered concomitant medications in one or both of the periods (Placebo-controlled Period and Open-label Period), depending on the (possibly imputed) start date, i.e. if the start date is at or after the date of Visit 5 IMP infusion, the medication is only considered ongoing in the Open-label Period.

15.15 Pooling Rule for the Country Variable for the Logistic Regression Models

In case of convergence, sparsity or separation issues, Firth's penalized likelihood method will be used. If it still fails to converge after Firth's penalized likelihood method applied, pooled country strategy will be used for analysis. Only a country with at least 5 participants is included as a standalone country. To avoid loss of information, small countries will be pooled from largest to smallest until there are 5 participants in the pooled country.

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17 Appendices

17.1 Schedule of Trial Procedures

Table 13 Trial Procedures and Assessments

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralized[c]	Withdrawal[d]
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoT Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
Screening and Baseline Procedures and Assessments									
Signed informed consent (including digital wearables)	√								
Demographics (age, sex, and race)	√								
Diagnosis (migraine and MOH)	√								
Disease-specific history[e]	√								
Relevant history (social, medical, psychiatric, neurological)	√								
Previous migraine and preventive medication use[e] including treatment failures	√								
Recent medication (prescription and non-prescription: traditional herbal medicines, non-pharmacological interventions, vitamins and mineral supplements)	√								
Height and weight	√								
Examinations (physical, neurological)	√								
Blood sampling for eligibility (including serology and other screening, for example β-HCG and FSH)	√								
Urine drug and alcohol screen	√								
ECG	√								
C-SSRS[f]	√								
Inclusion/exclusion criteria	√	√							
Signs and symptoms present at Screening and/or Baseline (before IMP intake) (recorded on an *Adverse Event Form*)	√	√							
Randomization		√							

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralizedc	Withdrawald
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoT Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
Efficacy Assessments (eDiary and ePROs[g])[h]									
eDiary recording[i]	√	√[j]	√	√	√[j]	√	√[k]		√[k]
eDiary compliance check[l]		√	√	√	√	√	√		
PGIC			√		√[j]		√		√
MBS	√	√[j]			√[j]		√		√
HADS		√[j]	√		√[j]		√		√
Digital device (optional)[m]	√	√	√	√	√[n]				√[n]
Pharmacoeconomic Assessments (ePROs[g])[h]									
HIT-6		√[j]	√		√[j]		√		√
mMIDAS		√	√		√		√		√
MSQ v2.1		√[j]	√		√[j]		√		√
EQ-5D-5L		√[j]	√		√[j]		√		√
HCRU		√[j]	√		√[j]		√		√
WPAI:M		√[j]	√		√[j]		√		√
TSQM-9		√[j]	√		√[j]		√		√
Safety Assessments									
Adverse events		√[o,p,q]	√	√	√[o,p,q]	√	√	√	√
Vital signs (including body temperature)	√	√[p,q]			√[p,q]		√		√

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralizedc	Withdrawald
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoT Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
Other Trial Procedures and Assessments									
Brief educational intervention[r], including SDS:H		√							
SDS:H					√				
IMP administered (intravenous infusion)[s]		√[o,t]			√[o,t]				
IMP accountability[u]		√			√				
Concomitant medication (prescription and non-prescription: traditional herbal medicines, non-pharmacological interventions, vitamins, and mineral supplements)		√[q]	√	√	√[q]	√	√	√	√
Substance use (alcohol, tobacco, caffeine, marijuana)	√	√	√	√	√				√[v]
eDiary training[h]	√								
ePRO training[h]	√								
eDiary closeout[k]							√		√
Pregnancy test[w]	√	√			√		√		√

β-HCG = human chorionic gonadotropin; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EoT = end of trial; eDiary = electronic diary; ePRO = electronic patient-reported outcome; EQ-5D-5L = Euroqol 5 Dimensions; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HCRU = Health Care Resource Utilization; HIT-6 = Headache Impact Test; IMP = investigational medicinal product; MBS = Most Bothersome Symptom; mMIDAS = modified Migraine Disability Assessment; MOH = medication overuse headache; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire Version 2.1; PGIC = Patient Global Impression of Change; PO = primary outcome; SDS:H = Severity of Dependence Scale Adapted for Headache; TSQM-9 = Treatment Satisfaction Questionnaire for Medicine – 9 items; WD = withdrawal; WPAI:M = Work Productivity and Activity Impairment questionnaire, Migraine version

a. All assessments may be completed over a maximum of 2 consecutive days with the exception of ePROs (see footnote g below); if so, the first day is considered the "visit" day according to the schedule.

b. If the date of an on-site visit or decentralized contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit. In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended by an extra period of seven days with approval from the

sponsor (the medical expert at H. Lundbeck A/S or the CRO's medical monitor) based on the provided rationale.

c. For decentralized visits, the participant will be contacted for eDiary compliance check, to ensure that the selected assessments have been completed and for collection of relevant information such as adverse events and concomitant medications.
d. Participants who withdraw their consent for trial participation should be withdrawn from the study. However, all efforts should be done to keep the participants who interrupted/terminated their IMP infusion in the trial and all assessments should be performed as described in the protocol. If participants want to withdraw from the study and thus not willing to attend the remaining visits as scheduled, they will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-up Visit at 20 weeks after administration of IMP.
e. Participants' available adequately documented records of migraine and MOH history and previous migraine preventive medication use (including treatment failures) within the 5 years prior to the Screening Visit.
f. The C-SSRS at Screening Visit will be administered by the authorized rater at the clinical site.
g. ePROs scheduled at Baseline Visit (Visit 2) and Week 12 Visit (Visit 5) must be completed in the clinical site on the visit date and before the infusion. ePROs which are scheduled in alignment with the Withdrawal Visit can be completed in the clinical site or in a remote setting within 3 days prior to the scheduled on-site visit date. ePROs which are scheduled in alignment with a decentralized contact must be completed in a remote setting and can be completed on the day or within 3 days prior to the scheduled decentralized contact date.
h. At the Screening Visit, the participant must be assisted with the provisioning and training of the eDiary and ePROs. Details will be provided in a separate user manual.
i. The eDiary assessments will be completed in the remote setting on a daily basis from Screening to EoT.
j. On the Baseline Visit and Week 12 Visit day, participants must complete the ePRO entries prior to infusion. Participants must ensure to complete eDiary recording of headaches that ended prior to infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary). For TSQM-9, due to no exposure of IMP prior to Baseline Visit, the assessment of overall IMP satisfaction with the TSQM-9 at Baseline visit will be used only as practice.
k. The eDiary closeout will take place at EoT Visit/Withdrawal Visit while the participant is at the clinical site. Details will be provided in a separate user manual.
l. In addition to the eDiary compliance checks performed at the defined on-site visits and decentralized contacts, ongoing evaluation of eDiary compliance will be performed by the site (based on eDiary reporting) and more frequent contact with participants may be needed in case of non-compliance.
m. At designated sites, the participants undergoing the additional actigraphy assessments must provide a signed digital device Informed Consent Form.
n. Hand in of Digital device. Participants undergoing the additional actigraphy assessments who drop out from the trial before Visit 5 must hand in the device at the Withdrawal Visit.
o. Infusion Related Reactions must be checked as part of the overall adverse event collection, during/after infusion and before the participant is discharged from the site.
p. Infusion must be preceded by the assessment of vital signs including body temperature, concomitant medications, and adverse events.

q. Vital signs including body temperature and adverse events must be checked after infusion.
r. The brief educational intervention must take place prior to IMP infusion.
s. An unblinded pharmacist or designee is responsible for receiving, storing and preparing IMP. The pharmacist or designee will not be responsible for other aspects of the clinical trial where blinding is necessary.
t. Participants must be monitored during and after the infusion in accordance with usual clinical practice.
u. A designated unblinded clinical research associate (CRA) is responsible for the IMP accountability.
v. Substance use will only be collected if the patient withdraws during the Placebo-controlled Period.
w. For women of childbearing potential, pregnancy test at the Screening Visit is to be conducted using serum β-HCG. At all other visits, where this is applicable the urine pregnancy testing will be performed using a urine stick test and in case of a positive finding, further confirmatory testing will be performed via serum β- human chorionic gonadotropin (β-HCG).

17.2 PCS Criteria for Vital Signs

Table 14 PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Variable	CDISC Term	Unit	PCS Low	PCS High
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Body Temperature	TEMP	ºC	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value.

17.3 Adverse Events of Special Interest

Table 15 Adverse Events of Special Interest

Event types	SMQ/HLT/HLGT	Additional criteria
Cardio/cerebrovascular events	Cardiac arrhythmias (SMQ) (Narrow)	
	Cardiac failure (SMQ) (Narrow)	
	Cardiomyopathy (SMQ) (Narrow)	
	Central nervous system vascular disorders (SMQ) (Narrow)	
	Embolic and thrombotic events (SMQ) (Narrow)	
	Hypertension (SMQ) (Narrow)	
	Ischaemic heart disease (SMQ) (Narrow)	
	Pulmonary hypertension (SMQ) (Narrow)	
	Torsade de pointes/QT prolongation (SMQ) (Narrow)	
Events associated with Suicide	Suicide/self-injury (SMQ) (Narrow)	
Events potentially associated with Trial Drug Infusion	Angioedema and urticaria (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Bronchial disorders (excl neoplasms) (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Infusion site reactions (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Oral soft tissue signs and symptoms (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Oral soft tissue swelling and oedema (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Pruritus NEC (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Rashes, eruptions and exanthems NEC (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Respiratory disorders NEC (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Respiratory tract signs and symptoms (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Upper respiratory tract disorders (excl infections) (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started

Event types	SMQ/HLT/HLGT	Additional criteria
Hepatic events	Drug related hepatic disorders - comprehensive search (SMQ) (Narrow)	
Hypersensitivity and Anaphylactic Reactions	Anaphylactic reaction (SMQ) (Narrow)	
	Angioedema (SMQ) (Narrow)	
	Hypersensitivity (SMQ) (Narrow)	
Seizures	Convulsions (SMQ) (Narrow)	

18 Changes to Analyses Specified in the Protocol

18.1 Definition of Trial Periods

The trial protocol term “safety follow-up period” will not be used when generating the output. Instead, the Open-label Period has been defined to also include collection of data at the Safety-Follow-up visit.

New definition of the Open-label Period: Starts at the beginning of Visit 5 IMP infusion (End of Week 12) and continues up to and including the Safety Follow-up visit (Week 32).

18.2 Objectives and Endpoints

For the primary objective, the following exploratory endpoints have been added:

- Change from baseline in number of days with auras without headache (Weeks 1-4, Weeks 1-12)
- Change from baseline in duration of severe pain (Weeks 1-4, Weeks 1-12)

For the secondary objective to evaluate the efficacy of eptinezumab during the 12-week Open-label Period, the following exploratory endpoints have been added:

- Change from baseline in number of days with auras without headache (Weeks 13-24)
- Change from baseline in duration of severe pain (Weeks 13-24)

For TSQM-9, due to no exposure of IMP prior to Baseline visit, the assessment of overall IMP satisfaction with the TSQM-9 appears to be not relevant to assess at Baseline visit and will be used only as practice. The secondary endpoint is updated to “Treatment Satisfaction Questionnaire for Medication – 9 items (TSQM-9) score at Week 4 and Week 12”.

18.3 Definition of a Migraine Day

For the definition of a migraine day it was clarified that a day with an aura without a headache for which migraine specific treatment was taken, is also considered a migraine day.

For exploratory analyses, two alternative definitions of a migraine day will be applied:

(1) a day will be qualified as a migraine day based on the symptoms and duration of the headaches occurring on that specific day only

(2) if a headache is lasting several days, all days on which this headache occurs will then be classified as a migraine day if the headache qualifies as a migraine using the approach number 1) for at least one of these days.

18.4 Definition of an eDiary Compliant Day

The definition will not be used.

18.5 Efficacy Analysis

18.5.1 General Efficacy Analysis Methodology

Only descriptive summaries will be presented for the efficacy analyses for the Open-label Period.

18.5.2 Country

Country will be added as a factor also in models for binary endpoints.

18.5.3 MMRM Model

Previous treatment failures-by-month interaction term is added in the MMRM model.

18.5.4 Binary Endpoints

A logistic regression model will be used for all the binary endpoints, except “Migraine on the day after dosing” (in accordance with protocol synopsis, but not protocol body).

18.5.5 Exploratory Endpoints

For analyses of passive registration of movement, “Minutes in no motion (0-10 a.U.)” is used to replace “Minutes in rest period (range 0-300, 101: rest epoch)”.

18.5.6 Subgroup Analyses

Due to a very low number of randomized participants from North America, the subgroup analysis by region (North America and Europe) specified in Section 16.8.9. in the trial protocol, will not be performed.