Statistical Analysis Plan

Interventional, randomized, double-blind, parallel-group, placebo-controlled delayed-start study to evaluate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache

Eptinezumab

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List of Abbreviations and Definitions of Terms

AESI	adverse events of special interest
ANCOVA	analysis of covariance
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS_DS	all-patients-treated in Delayed Start Period set
APTS_IN	all-patients-treated at interim set
ATC	anatomical therapeutic chemical
CI	confidence interval
DILI	drug-induced liver injury
eCH	Episodic Cluster Headache
IMP	investigational medicinal product
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MNAR	missing not at random
PCS	potentially clinically significant
pMI	placebo-based multiple imputation
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 Objectives

1.1 Primary Objective

To evaluate the efficacy of eptinezumab in patients with eCH.

1.2 Secondary Objectives

To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity.

1.3 Safety Objective

To evaluate the safety and tolerability of eptinezumab.

2 Study Design

This is an interventional, multi-regional, randomized, double-blind, placebo-controlled delayed-start study, designed to demonstrate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache (eCH).

An overview of the study is presented in Panel 1 and the scheduled study procedures and assessments are summarized in Appendix IV.

The target population for this study is defined as patients with eCH, based on the IHS ICHD-3 classification with a documented history of eCH of at least 12 months prior to Screening Visit 1, with a medical history of first symptoms of cluster headache from ≤60 years of age, with a prior history of cluster bout(s) lasting 6 weeks or longer when untreated, with minimum of at least 7 total cluster headache attacks out of the 7-day Screening Period 2 and a maximum of 56 cluster headache attacks out of the 7-day Screening Period 2, has demonstrated compliance with the eDiary by entry of data for at least 6 of the 7 days of Screening Period 2, and is aged ≥18 and ≤75 years at Screening Visit 1.

At the beginning of the 4-week Placebo-controlled Period (first part), 304 patients receive eptinezumab 400 mg or placebo according to the randomization (Infusion 1) in a 1:1 ratio. At the beginning of the second part of the study, starting with Infusion 2, patients that received placebo at Infusion 1 in the study will receive eptinezumab 400 mg. At the beginning of the second part of the study, starting with Infusion 2, patients that received eptinezumab 400 mg at Infusion 1 in the study will receive placebo but will continue to be exposed to eptinezumab following the 4-week Placebo-controlled Period due to the long half-life of eptinezumab (the exposure of eptinezumab is illustrated in Panel 1).

Patients will enter Screening Period 1 after Screening Visit 1. The patients can transition from Screening Period 1 to Screening Period 2 at any time during the first 52 weeks, as soon as they experience the beginning of a cluster headache bout, which is characterized by the

presence of at least one typical cluster headache attack, and not later than 1 week after the start of the first attack. For patients who enter the study already in cluster headache bout, Screening Visit 1 and Screening Visit 2 can be combined to capture all assessments for Screening Visit 1 and Screening Visit 2 on the same day.

Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enrol this patient in the study will be discussed with the investigator and the decision on whether to enrol the patient will be taken in the context of known history of typical duration of the bout for the individual patient.

Re-screening of patients will be allowed for patients who do not meet pre-defined specific eligibility criteria (details are presented in the study protocol).

Eligible patients will be randomly assigned to receive blinded treatment at the Baseline Visit (Day 0/Visit 3) with either eptinezumab 400 mg or placebo, administered as an IV infusion over 45 minutes (+15 minutes). Preferably the infusion should be administered in the morning.

All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (eptinezumab 400 mg or placebo), administered over 45 minutes (+15 minutes), at the end of Week 4 (Visit 6) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patients randomized to placebo will receive eptinezumab 400mg.

The Safety Follow-up Visit will take place at Week 24 (Visit 10), 20 weeks (5 half-lives) after the second IMP administration.

The total study duration from Screening Visit 1 to the Safety Follow-up Visit is up to 77 weeks and includes Screening Period 1 (up to 12 months / 52 weeks), Screening Period 2 (7 days), a Placebo-controlled Period (4 weeks), an Active Treatment Period (4 weeks), a Post-treatment Observational Period (8 weeks), and a Safety Follow-up Period (8 weeks).

Patients who withdraw from the study, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-Up Visit (SFU), scheduled 20 weeks after the last IMP administration.

Patients are allowed to withdraw from treatment and in this way not get the second infusion while staying in the study. The assessment from these patients will be handled according to section 13.3.2.

The following visits will be site visits: Screening Visit 1, Screening Visit 2, Baseline Visit (First Visit of the Placebo-controlled Period (Day 0/Visit 3) (randomization and IMP infusion)), Last Visit of the Placebo-controlled Period at the end of Week 4 (Visit 6 - second IMP infusion), Completion Visit at Week 16 (Visit 9) and SFU visit at Week 24 (Visit 10) or Withdrawal Visit, if applicable.

All other study visits will be phone contact visits.

In exceptional situations, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, site visits may only consist of blood sampling and urine sampling (for clinical laboratory tests, exploratory eptinezumab quantification, ADA including Nab, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse event recording, and IMP administration, while the remaining assessments (eDiary, ePROs, C-SSRS, and investigator evaluations) can be conducted remotely via a virtual clinic visit. These cases must be approved by the CRO's medical monitor.

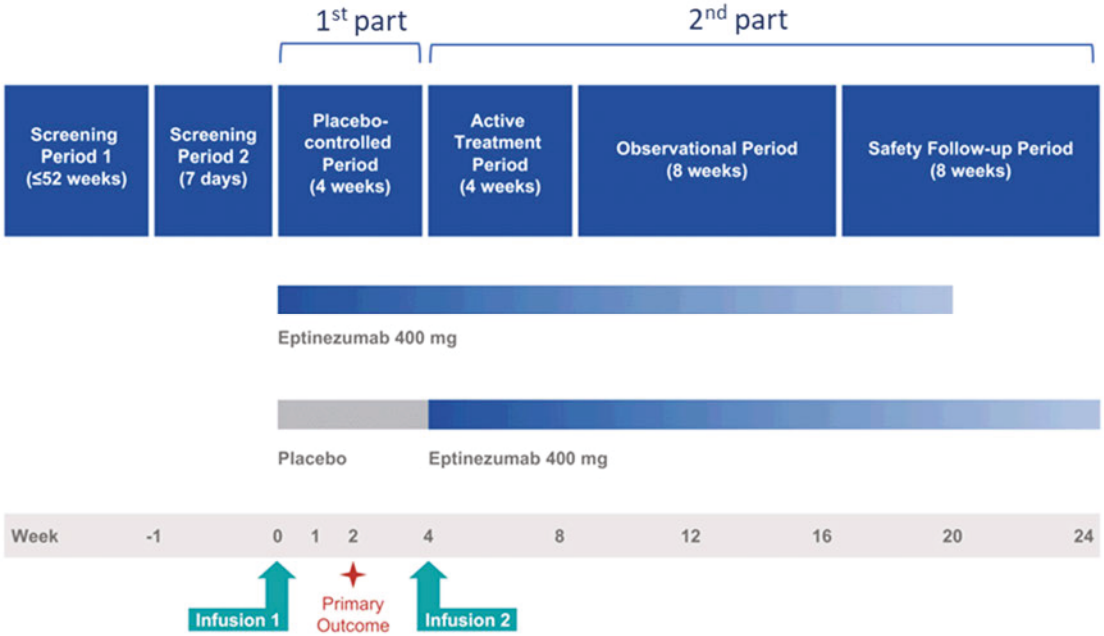
Patients will be assigned an eDiary at the Screening Visit 2 and will be required to complete this daily from the time of Screening Visit 2 until the Completion Visit (Week 16/Visit 9) or until the Withdrawal Visit.

During the study visits with IMP infusion, Vital Signs will be performed before and after the infusion. At these visits, AEs as well as safety laboratory tests, ECG, weight, and vital signs, including body temperature, will also be collected. Electronic patient-reported outcomes (ePROs) must be completed prior to infusion.

An interim analysis will be conducted for futility (see chapter 18).

In the charter for the interim analysis it is described that in case it was decided to stop recruitment based on the result of the interim analysis, no further patients would be treated with IMP. Patients that had received the first IMP infusion, but not the second at the time where it was decided to end recruitment, would not be given a second infusion and would be followed for 20 weeks after the IMP infusion instead of 24 weeks. These patients will attend the Week 8 Visit as planned but skip the Week 12 Visit assessments and have the Week 16 Visit procedures at Week 12 and the SFU visit at Week 20.

Panel 1 Study Design



In the Placebo-controlled Period (first part), patients receive eptinezumab 400 mg or placebo according to the randomization (Infusion 1). In the second part of the study, starting with Infusion 2, the patients who received eptinezumab 400 mg at Infusion 1 continue to be exposed to eptinezumab, but for blinding purposes they receive an infusion with placebo (Infusion 2), while the patients that received placebo at Infusion 1 receive eptinezumab at Infusion 2. The blue bars represent the total 20-week bioavailability of eptinezumab in the two groups.

3 Definitions

3.1 Definition of Baseline

Unless otherwise specified, the baseline value is the value captured either during the Screening Period 2 Visit or at the Baseline Visit prior to the infusion, whichever is later.

For the efficacy endpoints based on the eDiary, the data collected within the first 7 days of Screening Period 2 (the baseline period) will be used to calculate the baseline number of weekly events for the endpoints. In case of an extension of the Screening Period 2, the baseline number of weekly events will be calculated based on the first 7 days of the extended period, i.e. day 8-14.

See chapter 22 for handling of missing data.

3.2 Definition of Periods

The study consists of the following periods:

- *Screening Period 1* (1 day to 12 months / 52 weeks): Starts at the Visit 1 and continues up to but not including Visit 2

- *Screening Period 2* (7 days): Starts at Visit 2 and continues up to but not including Visit 3
- *Placebo-controlled Period* (4 weeks): Starts at Visit 3 IMP infusion and continues up to start of Visit 6 (2nd IMP infusion)
- *Active Treatment Period* (4 weeks): Starts at 2nd IMP infusion and continues up to but not including Visit 7
- *Post-treatment Observational Period* (8 weeks): Starts at Visit 7 and continues up to but not including Visit 9
- *Safety Follow-up Period* (8 weeks): Starts at Visit 9 and continues up to and including Visit 10

Unless otherwise specified, the Active Treatment Period, the Post-treatment observational Period, and the Safety Follow-up Period will be reported as one period called the *Delayed Start Period*.

For patients that were in the Placebo-controlled period, when the recruitment was stopped for futility, they are considered to be in the Delayed Start Period, from the time of their Week 4 Visit. In general, the term *treatment* will be understood as the *treatment sequence* if the period in scope also covers (parts of) the Delayed Start Period.

The definitions of these periods will in some cases differ from the description above depending on whether the assessments are efficacy or safety assessments. See further descriptions in chapter 22 for this.

3.3 Definition of Withdrawal

Any withdrawals from treatment after randomisation, but prior to the first infusion will be captured as withdrawal in the PBO-controlled Period, including the reason for withdrawal from treatment.

After receiving the first infusion, patients could withdraw from treatment and in this way not receive the second infusion. Due to the expected long duration of the treatment effect after the first infusion, this will be considered to only affect the treatment received in the Delayed Start Period, and thus it was not considered possible for patients to withdraw from treatment for the Placebo-controlled Period, although patients could withdraw from study during this period.

If a patient is withdrawn from the study and does not have a second infusion then the PBO-controlled period is not completed. If a patient is withdrawn from the study and has gotten the second infusion the PBO-controlled period is completed, but the Delayed-start Period is not.

If a patient is withdrawn from treatment and does not have a second infusion then the PBO-controlled Period is only completed if the patient did not withdraw from study in the PBO-controlled Period.

The group of patients withdrawn from treatment, prior to receiving the second infusion, will be described as *withdrawn from treatment*.

The group of patients withdrawn from study during the Placebo-controlled Period will be described as *withdrawn from study in the Placebo-controlled Period.* The group of patients that received both 1st and 2nd infusion and did not withdraw during the Placebo-controlled Period will be described as *completed the Placebo-controlled Period*.

The group of patients withdrawn from study in the Delayed Start Period will be described as *withdrawn from study in the Delayed Start Period.* The group of patients that received the second infusion and did not withdraw from study will be described as *completed the Delayed Start Period*.

For patients that were in the Placebo-Controlled Period when recruitment was stopped, they will be described as *completed the Placebo-controlled Period* if they have a Week 4 Visit or else they will be described as *withdrawn from study in the Placebo-controlled Period.* If the patients had a Week 4 Visit, they will be described as *withdrawn from study in the Delayed Start Period* if they were withdrawn or as *completed the Delayed start Period*, if they were not withdrawn in the Delayed Start Period.

3.4 Definition of Planned versus Actual Treatment

At baseline patients will receive either eptinezumab 400 mg or placebo in the Placebo-controlled Period. After 4 weeks of treatment in the Placebo-controlled period, patients previously randomized to eptinezumab will receive placebo and patients randomized to placebo will receive eptinezumab 400 mg in the Delayed Start Period.

The term treatment sequence will be used to denote the treatments arising by combining the treatments received in the Placebo-controlled Period and the treatments received in the Delayed Start Period (placebo-eptinezumab 400 mg / eptinezumab 400 mg-placebo), i.e. if all patients receive their treatment as planned, then the 2 groups reflecting the full treatment received are: placebo-eptinezumab 400 mg and eptinezumab 400 mg.

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

Actual treatment is defined as the treatment a patient actually received during the study. If a patient received a different treatment than what was planned at the first infusion, the actual treatment in the Placebo-controlled Period will equal that treatment. For the Delayed Start Period, if any patients by mistake receive eptinezumab 400 mg - eptinezumab 400 mg their actual treatment will be considered as eptinezumab 400 mg, and if any patients by mistake receive placebo - placebo their actual treatment will be considered as placebo, also for the Delayed Start Period.

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

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

To ensure that patients that were in the placebo-controlled period, when the recruitment was stopped are included in the tabulations, also the following categories will be summarized by planned treatment:

- Adverse events
- Exposure
- Safety laboratory parameters, vital signs, ECG, and C-SSRS

Unless otherwise specified, data listings will display actual treatment.

4 COVID-19

For this study, all patients are considered to have been enrolled after the beginning of the COVID-19 outbreak.

The following information is collected with regards to COVID-19:

- Whether a visit was done remotely due to COVID-19 including which assessments were/were not performed
- Whether patients withdrew due to the COVID-19 situation
- Whether patients got diagnosed with COVID-19

Specific output addressing the impact of COVID-19 for this trial is specified in chapter 8.

5 Endpoints

5.1 Primary Endpoint

Change from Baseline in the number of weekly attacks (Weeks 1–2).

5.2 Key Secondary Endpoints

- Response: ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2)
- Change from Baseline in the number of weekly times an abortive medication (triptans or O2) was used (Weeks 1-2)
- Change from Baseline in the number of daily attacks (Days 1-3)
- Change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)
- Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks)
- Number of attacks starting <=24 hours after the start of the first infusion of IMP

5.3 Secondary Endpoints

- Change from Baseline in the daily mean score on 5-point self-rating pain severity scale (Days 1-3)

- Change from Baseline in the number of weekly attacks (Week 1)
- Change from Baseline in the number of weekly attacks (Week 2)
- Response: ≥50% reduction from Baseline in the number of weekly attacks (Week 1)
- Response: ≥30% reduction from Baseline in the number of weekly attacks (Week 1)
- Response: ≥30% reduction from Baseline in the number of weekly attacks (Weeks 1-2)
- Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during the weeks).
- Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 1) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week).
- Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week).
- Change from Baseline in the number of weekly attacks (Weeks 1-4)
- Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-4) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during the weeks).
- Change from Baseline in the mean score on 5-point self-rating pain severity scale (average per attack over a week) for each of Weeks 1, 2, 3, and 4
- Change from Baseline in the number of weekly attacks for each of Weeks 3 and 4
- Patient Global Impression of Change (PGIC) score at each of Weeks 1, 2, and 4
- Change from Baseline in the Sleep Impact Scale (SIS) domain scores at each of Weeks 2 and 4
- Change from baseline in the EQ-5D-5L Visual Analogue Scale (VAS) score at Weeks 2 and 4
- Health Care Resources Utilization (HCRU) at Baseline and Week 4
- Change from Baseline in the Work Productivity Activity Questionnaire: General Health second version (WPAI:GH2.0) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Week 4

5.4 Exploratory Endpoints

- Response: ≥75% reduction from Baseline in the number of weekly attacks (Weeks 1-2)
- Change from Baseline in the number of weekly times an abortive medication (triptans or O2) was used (Weeks 1-4)
- Change from Baseline in the number of weekly times an abortive medication (triptans or O2) was used for each of weeks 1, 2, 3, and 4
- Time from first infusion of eptinezumab to resolution of cluster headache bout (within the first 16 weeks; only for patients randomized to eptinezumab at Baseline)
- Use (yes/no) of abortive medication (triptans or O2) for each of Weeks 5, 6 to 16
- Use (yes/no) of preventive medication for each of Weeks 1 to 16

- Use (yes/no) of transitional medication (GON block and oral steroids) for each of Weeks 5 to 16
- Number of attacks starting <= 24 hours of the start of the first infusion of IMP divided into three parts: one for attacks starting >=0 and <=8 hours after the start of the first infusion of IMP, one for attacks starting >8 and <=16 hours after the start of the first infusion of IMP, and one for attacks starting >16 and <=24 hours after the start of the first infusion of IMP
- Change from Baseline in the EQ-5D-5L Visual Analogue Scale (VAS) score at Weeks 8 and 16
- Patient Global Impression of Change (PGIC) score at Weeks 8 and 16
- Number of weekly attacks for each of Weeks 5 to 16
- Severity of pain (average per attack over a week) based on a 5-point self-rating pain severity scale for each of Weeks 5 to 16

5.5 Safety Endpoints

- Adverse events
- Absolute values and changes from Baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- Potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values
- Development of specific anti-eptinezumab antibodies (ADA) including neutralizing antibodies (NAbs)
- Columbia-Suicide Severity Rating Scale (C-SSRS) score

6 Analysis Sets

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

- all-patients-randomized set (APRS) - all randomized patients
- all-patients-treated set (APTS) - all patients in the APRS who received infusion with double-blind IMP
- all-patients-treated at interim set (APTS_IN) – all patients in the APRS who were among the first 204 that received infusion with double-blind IMP. Patients who received the infusion on the date where the infusion number 204 occurred, will also be included in the cut-off.
- all-patients-treated in Delayed Start Period set (APTS_DS) - all patients in the APTS who received an infusion with double-blind IMP at the Week 4 Visit and all patients in APTS that were in the Placebo-Controlled Period when recruitment was stopped and had a Week 4 Visit.

The efficacy analysis for the interim analysis will be based on the APTS_IN, and the final efficacy analysis will be based on the APRS. Demographics, baseline characteristics, and safety tables will be based on the APTS unless otherwise specified.

Two data point sets will be used for presenting the results:

- DPS1: All data points obtained at or after randomization
- DPS2: All data points obtained at or after randomization, but prior to patients receiving transitional medication (GON block and oral steroids) in the PBO-controlled Period. Only patients with a full start date of transitional medication will be candidates for exclusion from DPS2.

DPS1 will be used for all analyses, except for the sensitivity analysis of the primary endpoint addressing the effect of transitional medication, where DPS2 will be used.

A separate interim SAP will be prepared.

An interim Classification Meeting will be held after the database release for the patients fulfilling the criteria for participating in the interim analysis but before their blind is broken. At the interim Classification Meeting patients in the APRS that were among the first 204 infused (Infusion I) and those who received the Infusion I on the date where the infusion number 204 occurred, will be classified into analysis sets.

When all in patients in APRS have had the chance of completing the Placebo-controlled Period (Visit 6/Week 4), data collected in the Placebo-controlled Period will be cleaned and locked.

A Classification Meeting will be held after the database release for the reporting of the Placebo-controlled Period but before the blind has been broken. Patients included in the interim cut-off will not be re-classified. Any data points excluded from DPS2 will be identified and recorded. Analyses specified in the SAP for data collected in the Placebo-controlled Period will then be performed.

After all patients have completed the study, data will be cleaned and locked, the database will be released and the remaining analysis in the SAP will be performed.

Investigators and patients will be informed about which treatment (eptinezumab 400 mg or placebo) the patients received in the Placebo-controlled Period only after the last patient has completed the study.

7 Descriptive Statistics

Unless otherwise specified, summary statistics (numbers, 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 categorical variables.

Unless otherwise specified, data listings will include site, treatments, patient screening number, sex, age, race, and baseline weight.

8 Patient Disposition

8.1 Summary of Patient Disposition

Patient disposition will be summarized by treatments, and by site and treatments, and include the number of patients in each analysis set defined in chapter 6, and the number of patients in the APTS who completed or withdrew. The summary will be done for the Placebo-controlled Period and for the subsequent Delayed Start Period for APTS_DS.

To assess the potential impact of COVID-19 on the visit structure, a table will be provided by type of visit (on site or remote) and treatment separately for each period, for the visits that are changed from on site to remote. The summary will be based on APTS.

8.2 Withdrawals

The number of patients who withdrew from study during the Placebo-controlled Period and the number of patients who completed the Placebo-controlled Period will be summarized by treatment, and the withdrawals from study will also be summarized by treatment and primary reason for withdrawal, and by treatment, and all reasons for withdrawal.

The number of patients who withdrew from treatment will be summarized by treatment and primary reason for withdrawal, and by treatment and all reasons for withdrawal.

The number of patients who withdrew from study during the Delayed Start Period and the number of patients who completed the Delayed Start Period will be summarized by treatment, and the withdrawals from study will also be summarized by treatment and primary reason for withdrawal, and by treatment, and all reasons for withdrawal.

Patients who withdrew from study and patients who withdrew from treatment will be listed and the listing will include the number of days in the study until withdrawal, the number of days since the last IMP infusion, treatment period, the primary reason for withdrawal, all reasons for withdrawal, and a flag if the drug code was broken.

If needed, a listing of patients who withdrew due to COVID-19 situation (as the primary reason) will be provided as well as a listing of patients withdrawing due to falling ill of COVID-19 (as the primary reason). The latter is defined as patients withdrawing due to an adverse event, which is then specified to be COVID-19.

Kaplan-Meier failure plots of time to withdrawal from study will be presented by treatment period (that is, for the Placebo-controlled Period alone by treatment and for the period from Baseline to week 16). The time will be calculated from the date of first dose of IMP in the treatment period to the date of completion or withdrawal from study within the specified treatment period. Patients who completed study will be regarded as censored.

All tables and graphs will be based on the APTS. Listings will be based on the APRS.

9 Demographics and Baseline Characteristics

Demographics (sex, age, race, region, country); baseline characteristics (height, weight, and BMI); and baseline efficacy variables will be summarized for the Placebo-controlled Period by treatments. Also family history of eCH will be summarized by treatment group.

Baseline disease characteristics (Time since 1st symptoms of CH, Time since CH diagnosis, any previous change over time for the CH phenotype (categories No, from chronic to episodic, or from episodic to chronic to episodic), Time since start of last bout, Duration of last bout, Approximate number of bouts per year, Ability to predict a bout, Seasonal bout, Usual start time of attacks, Usual duration of the bout (in weeks), Usual number of attacks / day, Usual duration of the attacks (in min), Usual duration of the remission period (in months), and the accompanying symptoms; will be summarized by treatment.

The eDiary reported baseline efficacy variables that will be summarized are the baseline number of weekly attacks, baseline number of times abortive medication was used and baseline weekly integrated measure of frequency and intensity of pain, baseline daily mean pain score, which are all collected during the Screening Period 2.

Other baseline efficacy variables that will be summarized are: SIS, EQ-5D-5L (the visual analogue scale (VAS) of the overall health state), HCRU, and WPAI:GH2.0.

Treatment failure medication, type of failure, and number of previous treatment failures will be summarized by treatment.

Concurrent as well as relevant past medical, neurological, and psychiatric disorders will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarized by treatment. Social history will be summarized by treatment.

A concurrent medical, neurological, or psychiatric disorder is a disorder that is ongoing at the Screening Visit 2. A past medical, neurological, or psychiatric disorder is a disorder that ended prior to the Screening Visit 2.

Demographics, baseline characteristics, and baseline disease characteristics will be summarized based on the APTS, and baseline efficacy variables will be summarized based on the APRS.

10 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the WHO Drug Dictionary (WHO-DDE).

For the Placebo-controlled Period medications will be classified according to the start and stop time for the period and summarised by anatomical therapeutic chemical (ATC) code and generic drug name, and treatment:

- medication discontinued prior to the date of first IMP infusion

- concomitant medication taken in the Placebo-controlled Period:

  Medications with a start date at or after the date of first IMP infusion and prior to the date of second IMP infusion, medications with a stop date at or after the date of first IMP infusion that also have a start date prior to the date of second IMP infusion, and medications where both start and stop date are completely missing. Ongoing medications with a start date prior to the date of second IMP infusion are also included, as well as medications with a start date prior to the date of second IMP infusion with a completely missing stop date. For patients that were in the Placebo-Controlled Period when recruitment was stopped, the start day should be prior to the Week 4 Visit date instead of prior to the second IMP infusion.

For the Delayed Start Period combined, medications will be classified according to the start and stop time for the period and summarised by anatomical therapeutic chemical (ATC) code and generic drug name, and treatment:

- concomitant medication continued after the date of second IMP infusion, or after the date of the Week 4 Visit for patients that were in the Placebo-controlled Period when recruitment was stopped.
- concomitant medication started at or after the date of second IMP infusion and before the study end date, or at or after the date of the Week 4 Visit and before the study end date for patients that were in the Placebo-controlled Period when recruitment was stopped..

All disallowed medications will be listed based on the APRS. The listing will include the generic drug name, the duration, the start and end dates, and dosing information.

For the reporting of preventive and abortive medication for treatment of CH, the following will be reported:

- Number of patients taking abortive medication will be summarized for baseline period, Placebo-controlled period, and Delayed Start Period.
- Number of patients using preventive medications will be summarized for the baseline period and the Placebo-controlled period, and the total number of patients using preventive medications will also be summarized.

Previous use of medication medication for treatment of CH will be summarized by treatment.

Number of patients using transitional medications (GON block and oral steroids) will be summarized for the Delayed Start period. If transitional medications (GON block and oral steroids) are used in the Placebo-controlled Period, the cases will be listed.

11 Exposure

For each period, the number of infusions received, the number completed as planned, the number interrupted and re-started, and the number that lasted longer/less than 45 (+15) minutes will be summarized by treatment.

Patients, who at any point during the study received a different treatment than what was planned, will be listed. The listing will include all infusion visits, dates of infusion visits, planned treatment for the patient and actual treatment received for the patient.

In addition, all infusion data will be listed, i.e. the start and stop time of the infusion and the duration of the infusion.

12 eDiary Compliance

The proportion of days with non-compliance with the eDiary will be summarized and presented by 1-week interval and treatment for each period. Furthermore, the number of patients missing 4 days or more in a 7-day period will be presented by 1-week interval and treatment for each period.

A day of non-compliance is defined as a day where the subject did not report any attacks in the eCH eDiary, and also did not confirm no attacks in the evening eDiary.

The summaries will be based on the APRS.

13 Efficacy

13.1 General Efficacy Analysis Methodology

Unless otherwise specified, all efficacy analyses will be based on the APRS.

All tables and graphs will be presented by treatment.

All p-values will be based on two-sided tests; the endpoints will be presented with two-sided 95% confidence intervals (CIs). The endpoints not included in the testing strategy will be presented with p-values and 95% CIs.

Apart from the exploratory endpoint ‘Time from infusion to resolution of cluster headache bout within 16 weeks’ which will only be presented for patients randomised to eptinezumab during the placebo-controlled phase, the efficacy data from the Delayed start period (excluding the safety follow-up period) will only be presented descriptively.

13.2 Testing Strategy

Primary endpoint:

- Change from Baseline in the number of weekly attacks (Weeks 1-2)

Key secondary endpoints in hierarchical order:

- Response: ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2)

- Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2)
- Change from Baseline in the number of daily attacks (Days 1-3)
- Change from Baseline in the number of weekly days with < 3 attacks per day (Weeks 1-2)
- Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks)
- Number of attacks starting <=24 hours after the start of the first infusion of IMP

A two-sided significance level of 5% will be used for the formal hierarchical testing strategy.

The testing strategy will be a sequence of tests, testing one endpoint at a time. Only if one step has shown a statistically significant effect will the formal testing continue with the next step, thus ensuring protection of the type 1 error. The steps are described below.

Step 1

Test the primary endpoint using a 5.0 % significance level. If the primary endpoint shows an advantageous effect of eptinezumab compared to placebo, the effect seen for the primary endpoint is considered statistically significant, and the testing continues with the next step.

Step 2

Test the first key secondary endpoint using a 5.0% significance level. If the first key secondary endpoint shows an advantageous effect of eptinezumab compared to placebo, the effect seen for the first key secondary endpoint is considered statistically significant, and the testing continues with the next step for the second key secondary endpoint.

Step 3

The steps for testing the key secondary endpoints in the order stated in the beginning of this section continues until a p-value >= 0.05 is encountered or all 6 key secondary endpoints are found to be statistically significant.

13.3 Analysis Methodology for the Primary Endpoint

13.3.1 Primary Estimand

The primary estimand will be the mean difference in change from Baseline in the number of weekly attacks (Weeks 1-2) between patients with episodic cluster headache treated with eptinezumab and placebo, without use of transitional medication (GON block and oral steroids), and regardless of use of abortive or preventive medication, and infusion interruption or termination before full dose is received.

Intercurrent Events

The following intercurrent events, occurring after treatment initiation and potentially affecting either the interpretation or the existence of the measurements associated with the clinical question of interest, are considered:

- Transitional medication for cluster headache (GON block and oral steroids)
- Interruption of IMP: Infusion stopped prematurely

Attributes of the primary estimand

The primary estimand has the following attributes:

- The **treatment condition of interest** will be the comparison of eptinezumab to placebo without the use of transitional medication (GON block and oral steroids), and with or without the use of abortive or preventive medication for cluster headache
- The **population of interest** will be all patients with episodic cluster headache that fulfil the inclusion and none of the exclusion criteria
- The **endpoint to be obtained to address the clinical question** is change from Baseline in the number of weekly attacks (Weeks 1-2)
- The **intercurrent events:** use of transitional medication (GON block and oral steroids) or interruption or prematurely stopping IMP infusion will be addressed by treatment policy strategies
- The **population level summary** will be the mean difference in the primary endpoint between eptinezumab and placebo.

13.3.2 Rationale for the Primary Estimand

The number of weekly attacks is considered a good measure of the disease burden in episodic cluster headache and therefore will be used for the primary endpoint.

Justification of Treatment Condition of Interest

The use of abortive medication (triptans and O2) is included in the treatment condition of interest because abortive medication is taken after an attack begins to affect that specific attack. It is not expected that the use of abortive medication will affect the number of attacks following an attack where abortive medication was taken. Thus, the use of abortive medication is not considered to be an intercurrent event.

The use of preventive medication is included in the treatment condition of interest because eptinezumab is expected to be used with or without other preventive medication for patients suffering from episodic cluster headache. Furthermore, though the use of preventive medication could influence the number of attacks, the potential effect is expected to be limited in an episodic cluster headache population. Thus, the use of preventive medication is not considered to be an intercurrent event.

Intercurrent events:

- Use of transitional medication (GON block and oral steroids) for cluster headache – addressed by a treatment policy strategy

  The treatment effect of interest is in patients without use of transitional medications, since the treatment is mainly considered as an alternative rather than an add-on to transitional medication. Use of transitional medication is disallowed from 30 days prior to first IMP and for the first 4 weeks after first IMP according to the protocol, meaning that the collected data in this way will estimate the effect in patients without use of transitional medications during the Placebo-controlled Period. Should transitional medication be used during the first 4 weeks after first IMP, despite it being disallowed, it will be addressed using a treatment policy strategy.

- Interruption or prematurely stopping IMP infusion – addressed by a treatment policy strategy

  The primary estimand targets the effect seen regardless of interruption or prematurely stopping IMP infusion. This is considered a conservative approach, as such disturbances are mainly expected to affect the active treatment.

13.3.3 Primary Analysis

The clinical question of interest is whether the number of attacks is reduced more with eptinezumab than with placebo during the first 2 weeks after infusion.

The primary endpoint, that will address the clinical question of interest, will be the change from Baseline in the number of weekly attacks (Weeks 1-2). The endpoint is based on eDiary data on attacks and the average number of weekly attacks across Week 1 and Week 2 will be estimated as presented below.

The strategy for imputation of missing data is given below and in details in chapter 22:

1. For each weekly score, including the Baseline Period, prorating is used to impute any missing data where the eDiary is completed on at least 4 out of the 7 days, to have full weekly scores
2. For patients with ≤3 days with observations during the Baseline Period, the missing baseline number of weekly attacks will be drawn from a normal distribution with the mean and SD taken from the baseline number of weekly attacks for patients where a baseline number of weekly attacks has been obtained (from patients with at least 4 of 7 days of observations and possibly using prorating for the calculation). If needed, this step will be incorporated as the initial step of the placebo-based multiple imputation (pMI) analysis, and thus new random baseline values will be drawn for each of the 200 simulated data sets, in case of missing baseline values, see Appendix II.

The primary analysis will use a pMI-method. Specifically, an analysis will be performed using a pattern-mixture model (PMM), in which after application of the prorating rule to data, any missing weekly scores will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the placebo group.

The pMI will generate 200 simulated data sets with complete assessment of number of weekly attacks for Weeks 1, 2, 3, and 4. For details on potential missing baseline scores please see section 23.1.1.1.

The steps of the multiple imputation analysis using trajectory of the placebo treatment will be the following:

1. Use SAS PROC MI using MCMC to generate 200 data sets and ensure that all patients only have monotone missing data, using a seed of 210876[1]
2. Use SAS PROC MI with monotone regression to complete the 200 data sets where the missing data for weekly scores are imputed MNAR according to the placebo treatment both for patients randomised to eptinezumab and placebo, using a seed of 67653179[2]
3. Analyse each of the data sets according to the MMRM model described below
4. Use SAS PROC MIANALYZE to combine the results from the 200 analyses according to Rubin's Rule

SAS code that illustrates the key steps of the pMI analysis above is shown in Appendix II.

From the pMI analysis, the estimate, standard error, 95% confidence interval, t-test statistic and p-value will be presented.

MMRM model

The MMRM model will analyse the change from Baseline in the number of weekly attacks using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach.

The MMRM model based on data from all 4 weeks in the PBO-controlled period will include the following fixed effects: week (1, 2, 3, 4), country, and treatment as factors, baseline score as a continuous covariate, treatment-by-week interaction, and baseline score-by-week interaction. An unstructured variance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The mean difference between eptinezumab and placebo in the Change from Baseline in the number of weekly attacks (Weeks 1-2) will be estimated based on least square means for the treatment-by-week-interaction, using weights (1/2 1/2 0 0) for the eptinezumab by week estimates, and weights (-1/2 -1/2 0 0) for the placebo by week estimates. The SAS® code for the MMRM model is shown in Appendix II.

To investigate the impact of the missing not at random (MNAR) assumption used for the primary analysis, an additional sensitivity analysis will be performed in which a similar multiple imputation analysis will be conducted as for the primary endpoint, but where missing data will be imputed according to the randomised treatment with eptinezumab or placebo. The mean difference between eptinezumab and placebo in the Change from Baseline in the

[1] The seed 295802 was used for the interim analysis

[2] The seed 73128522 was used for the interim analysis

number of weekly attacks (Weeks 1-2) will be estimated based on least square means for the treatment-by-week-interaction, using weights (1/2 1/2 0 0) for the eptinezumab by week estimates, and weights (-1/2 -1/2 0 0) for the placebo by week estimates.

The primary analysis will be based on the APRS, using the DPS1 Data point set, with all observations included.

13.3.4 Rationale for Selected Analysis Method for the Primary Endpoint

The data from the eDiary will be imputed according to the rule above using prorating (see section 23.1.1.2), and then analysed using the above described pMI model.

The MMRM model is chosen as it is a very flexible and robust analysis, and with the selected explanatory variables it will allow treatment to vary freely by week, account for the baseline level and for the stratification by country, and include the most flexible structure for within patient variation.

The multiple imputation analysis will ensure that all randomised patients are included in the primary analysis, and the strategy chosen will impute missing data for patients treated with eptinezumab, as if they were treated with placebo, to ensure that the result of the primary analysis likely will be conservative.

13.3.5 Sensitivity Analyses of the Primary Endpoint

13.3.5.1 Sensitivity Analyses to assess the impact of missing observations

To assess the impact of imputing missing observations on eptinezumab based on the placebo treatment, the MMRM model described above will be used to analyse the data, where prorating has been used for weekly scores with at least 4 days with observations, but where no further imputations have been performed.

The mean difference between eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-week interaction in the MMRM model. The mean difference between eptinezumab and placebo in the Change from Baseline in the number of weekly attacks (Weeks 1-2) will be estimated based on least square means for the treatment-by-week-interaction, using weights (1/2 1/2 0 0) for the eptinezumab by week estimates, and weights (-1/2 -1/2 0 0) for the placebo by week estimates. The estimates will be presented with p-values and 95% CIs.

13.3.5.2 Sensitivity analysis to assess the impact of use of transitional medication for eCH

Transitional medications (GON block and oral steroids), which are often used during a time where the effect of the currently available preventive medication has not yet set in and can hence be considered as a type of rescue medication, could potentially end the bout of cluster headaches and hence the treatment effect is considered relevant if it is seen in patients without

the use of transitional medications. Thus, a sensitivity analysis is added to more precisely assess the effect under such circumstances, by considering the impact of including data after the use of transitional medication.

The impact of use of transitional medication (GON block and oral steroids) for cluster headaches will be addressed under a hypothetical strategy of no transitional medication being available. Under these hypothetical circumstances it is assumed that the effect would be similar to other patients with similar previous scores in the placebo treatment, and the analysis will be conducted by removing any eDiary data in the PBO-controlled Period after the use of transitional medication, as thus use APRS but for the DPS2 data point set, only including data points obtained at or after randomization, but prior to patients receiving transitional medication (GON block and oral steroids). Based on this data, the prorating will be re-done to generate a new data set (see details in section 23.1.1.3). The new data set will be analysed using the MMRM model described in the primary analysis section.

13.4 Analysis Methodology for the Key Secondary Endpoints

13.4.1 Analysis of the Key Secondary Endpoints

The testing strategy for the key secondary endpoints is described in section 13.2.

13.4.1.1 Continuous endpoints

The estimands for the continuous endpoints: Change from Baseline in the number of daily attacks (Days 1-3), Change from Baseline in the number of weekly days with < 3 attacks per day (Weeks 1-2), and Number of attacks starting <=24 hours after the start of the first infusion of IMP share 4 attributes:

- The **treatment condition of interest** will be the comparison of eptinezumab 400 mg to placebo without the use of transitional medication (GON block and oral steroids), and with or without the use of abortive or preventive medication for cluster headache
- The **population of interest** will be all patients with episodic cluster headache that fulfil the inclusion and exclusion criteria
- The **intercurrent events:** use of transitional medication (GON block and oral steroids) or interruption or prematurely stopping IMP infusion will be addressed by a treatment policy strategy
- The **population level summary** will be the mean difference in the endpoint between eptinezumab 400 mg and placebo.

In addition, the endpoint Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2) shares the same attributes, with the exception of the following:

- The **treatment condition of interest** will be the comparison of eptinezumab 400 mg to placebo without the use of transitional medication (GON block and oral steroids) and with or without the use of preventive medication for cluster headache

The endpoints used for the 4 continuous endpoints are the following:

- The **endpoint to be obtained to address the clinical question** is the change from Baseline in the number of weekly times an abortive medication (triptans or O2) was used (Weeks 1-2)
- The **endpoint to be obtained to address the clinical question** is the change from Baseline in the number of daily attacks (Days 1-3)
- The **endpoint to be obtained to address the clinical question** is the change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)
- The **endpoint to be obtained to address the clinical question** is the number of attacks starting <=24 hours after the start of the first infusion

The continuous key secondary endpoints (Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2), and Change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)) will be analysed using a single MMRM model (without multiple imputation) as presented in section 13.3.3 on primary analysis using the baseline value of the variable as baseline.

The Change from Baseline in the number of daily attacks (Days 1-3) will be analysed using an analysis of covariance (ANCOVA) including treatment and country as factors and baseline number of daily attacks as covariate.

The Number of attacks starting <=24 hours after the start of the first infusion of IMP will be analysed using an ANCOVA with treatment and country as factors and with the baseline number of weekly attacks as covariate.

13.4.1.2 Response: ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2)

The estimand attributes are the following:

- The **treatment condition of interest** will be the comparison of eptinezumab 400 mg to placebo without the use of transitional medication (GON block and oral steroids) and with or without the use of abortive or preventive for cluster headache
- The **population of interest** will be all patients with episodic cluster headache that fulfil the inclusion and exclusion criteria
- The **endpoint to be obtained to address the clinical question** is patients with ≥50% reduction from baseline in the number of weekly attacks (Weeks 1-2)
- The **intercurrent events:** use of transitional medication (GON block and oral steroids) or interruption or prematurely stopping IMP infusion will be addressed by a treatment policy strategy
- The **population level summary** will be the odds ratio for the endpoint between eptinezumab 400 mg and placebo.

The patients with ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2) endpoint will be analysed using logistic regression where region and treatment are included as fixed factors and baseline number of weekly attacks is included as covariate.

13.4.1.3 Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks)

Resolution is defined as the day after the last day with cluster headache attacks of moderate, severe, or excruciating pain or where abortive medication (triptans or O2) was used (whichever is the latest), when this is followed by a 2-week period free of cluster headache attacks or with cluster headache attacks with only mild pain, not requiring the use of abortive medication, where both weeks in the 2-week period had at least 4 days of eDiary compliance. The 2-week period free of attacks or with only mild pain or No pain/Barely any pain are allowed to start on any day within the period, and not confined to Day 1, Day 8 etc. Patients that do not obtain resolution of bout are censored at the last time point that is followed by 2 periods of a week each, with at least 4 days of eDiary compliance. For the analysis of time to resolution of cluster headache bout within the first 4 weeks, the latest time point for censoring will be Day 28.

The estimand attributes are the following:

- The **treatment condition of interest** will be the comparison of eptinezumab 400 mg to placebo without the use of transitional medication (GON block and oral steroids) and with or without the use of preventive medication for cluster headache
- The **population of interest** will be all patients with episodic cluster headache that fulfil the inclusion and exclusion criteria
- The **endpoint to be obtained to address the clinical question** is time from first infusion to resolution of cluster headache bout within the first 4 weeks
- The **intercurrent events:** use of transitional medication (GON block and oral steroids) or interruption or prematurely stopping IMP infusion will be addressed by a treatment policy strategy
- The **population level summary** will be the hazard ratio for the endpoint between eptinezumab 400 mg and placebo.

Time from infusion to resolution of cluster headache bout within the first 4 weeks will be analysed using a Cox regression model with baseline number of weekly attacks as covariate and treatment and length of Screening Period 2 (1 or 2 weeks of screening period 2) as fixed factors.

13.4.2 Rationale for Selected Analysis Method for the Key Secondary Endpoints

The MMRM model is chosen as it is a very flexible and robust analysis, and with the selected explanatory variables it will allow treatment to vary freely by week, account for the baseline level and for the stratification by country, and include the most flexible structure for within patient variation.

The logistic regression model has been chosen for its ability to provide estimates of treatment effects, as well as adjust for the effects of strata and covariates. Covariates are included in the model based on an approach including key factors representing study design features/strata (region and treatment), and baseline number of attacks to account for its predictive ability.

The chosen covariate and fixed factors are considered to be highly predictive, and thus the logistic regression model is considered as appropriate.

For the time from infusion to resolution key secondary endpoint the rationale for selecting Cox regression model is that it is an analysis for time-to-event endpoints that allows for the possibility of adjusting for covariates. The selected explanatory variables are expected to be relevant predictors of resolution.

13.4.3 Sensitivity Analyses of the Key Secondary Endpoints

For endpoints where data imputation is used, the impact of the imputations will be assessed in sensitivity analyses, applying different methods of imputation:

Change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)) will be analysed using the same principles for the pMI (but with a new seed) as presented in section 13.3.3 on primary analysis using the baseline value of the variable as baseline.

For the time from infusion to resolution key secondary endpoint the Cox regression model described in section 13.4.1.3 will be repeated with survival data generated requiring at least 5 days of eDiary compliance within each week. In addition, the analysis will be repeated using data censored at the day before use of transitional medication (GON block and oral steroids).

For the binary response key secondary endpoint, the logistic regression model will be run on data where patients using transitional medication (GON block and oral steroids) is considered as non-responders.

In addition, the ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2) endpoint will be calculated for the 200 data sets generated for the pMI analysis for the primary endpoint and analysed using the specified logistic regression. The results will be weighted together using the approach by Ratitch et al.[1]

13.5 Analysis of the Secondary Endpoints

The continuous secondary endpoints (with the exception of PGIC, HCRU, and Change from Baseline in the daily mean score on 5-point self-rating pain severity scale (Days 1-3)) will be analysed using an MMRM model (without multiple imputation) similar to the one described in the primary endpoint section.

The PGIC score will be analysed using an MMRM (without multiple imputation) with number of attacks in the Screening Period 2 as covariate instead of baseline score.

The Change from Baseline in the daily mean score on 5-point self-rating pain severity scale (Days 1-3) will be analysed using an ANCOVA including treatment and country as factors and baseline as covariate.

Tables displaying the counts and percentage of answers to each category of response options for each item of EQ-5D-5L will be presented by visit and treatment. Furthermore, shift tables

displaying for each item in EQ-5D-5L the number and percentage of patients who decreased, increased or had no change from baseline in the item score will be provided by visit and treatment.

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

Descriptive tables displaying the counts and percentage of the weekly integrated measure of frequency and intensity of pain at each week will be provided by treatment.

The binary secondary endpoints (response) will be analysed in a similar way as for the key secondary endpoint using a logistic regression with region and treatment included as fixed factors and baseline number of weekly attacks as a covariate.

13.6 Analysis of the Exploratory Endpoints

The continuous exploratory endpoints will be analysed using an MMRM (without multiple imputation) model similar to the one described in the primary endpoint section.

The binary exploratory endpoint (response) will be analysed in a similar way as for the key secondary endpoint using a logistic regression with region and treatment included as fixed factors and baseline number of weekly attacks as a covariate.

A Kaplan-Meier plot of time from infusion to resolution of cluster bout within 16 weeks will be provided for the 400 mg eptinezumab treatment. See section 23.1.1.5 for details on the endpoint.

The ANCOVA model used for analysing number of attacks starting within 24 hours of the start of the first infusion, described in section 13.4.1.1 will be implemented for data assessed in 3 different time intervals after the first infusion giving 3 different treatment estimates: one for attacks starting 0-8 hours after the first infusion, one for attacks starting 8-16 hours after first infusion, and one for attacks starting 16-24 hours after the first infusion.

The following endpoints will be presented using descriptive statistical analyses:

- Use (yes/no) of abortive medication (triptans or O2) for each of Weeks 5, 6, …, 16
- Use (yes/no) of preventive medication for each of Weeks 1, 2, …, 16
- Use (yes/no) of transitional medication (GON block and oral steroids) for each of Weeks 5, 6, …, 16
- Change from Baseline in the EQ-5D-5L Visual Analogue Scale (VAS) score at each of Weeks 8 and 16
- Patient Global Impression of Change (PGIC) score at each of Weeks 8 and 16
- Number of weekly attacks for each of Weeks 5, 6, …,16
- Severity of pain (average per attack over a week) based on a 5-point self-rating pain severity scale for each of Weeks 5, 6, …, 16

13.6.1 Covariate Investigation and Subgroup Analyses

The assumption of equal treatment effect across subgroups will be investigated on an exploratory basis for all subgroups listed above by adding the three-way interaction term subgroup-by-treatment-by-week to the MMRM model described in section 13.3.3 using the DPS1 data. A test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the MMRM-model will be performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term.

This will be done by fitting both models using (maximum likelihood) ML and making a likelihood ratio test comparing -2*log(Q) to the asymptotic X^2 distribution, where Q is the quotient of the maximised likelihood functions. The p-value for this test will be reported.

Among the subgroups to be investigated are:

- Age category (≤ 45, > 45)
- Age category at first symptoms (<25, 25-45, and >45)
- Previous treatment failures (≤ 3, > 3)
- Sex
- Race (White, Other)
- Region
- Baseline severity (≤ 14 baseline attacks, > 14 baseline attacks)
- Duration of the CH history (time since the first symptoms of the disease) at study entry determined at Screening Period 2 (<= median, > median)
- Use of preventive medication at study start at Screening Period 2

The primary analysis using pMI will be repeated for each of the subgroups mentioned above, based on the same 200 imputed data sets.

14 Safety

14.1 Adverse Events

14.1.1 General Methodology for Adverse Events

All the tables and graphs will be presented by treatment.

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order based on the percentages of patients with these adverse events in the eptinezumab 400 mg dose group.

Unless otherwise specified, the summaries of adverse events will include the number and percentage of patients with an adverse event, and the total number of events.

Listings of adverse events will be sorted by site, treatment, patient screening number, baseline weight, age, sex, treatment period, and adverse event start date, and include preferred term, investigator term, adverse event start date and time and period, days since first dose of IMP, date/start time/stop of IMP, Days since last start of IMP, duration of the adverse event, date of death (if applicable), action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included. Start and stop dates imputed to document classification of patients will not be displayed in the listings of adverse events.

14.1.2 Coding of Adverse Events

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

14.1.3 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 patient re-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. Note that for an adverse event with an incomplete start date, only the date itself will be imputed and used for classification of treatment-emergent status, i.e. the time of the infusion will not be taken into account when classifying adverse events with incomplete start dates and thus such an adverse event will be classified as treatment-emergent simply if the imputed start date is on or after the date of first IMP infusion.

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, then the AE is considered causally related.

14.1.4 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 or increases in intensity or becomes serious during or after the time of infusion of IMP in the Placebo-controlled Period and before the date and time of the infusion of IMP in the Active Treatment Period. For patients that were in the Placebo-Controlled Period when recruitment was stopped, a TEAE in the Placebo-Controlled Period is defined as a TEAE that starts or increases in intensity or becomes serious during or after the time of infusion of IMP in the Placebo-Controlled Period and before the date of the Week 4 Visit.

- *TEAE in the Delayed Start Period* – a TEAE that starts or increases in intensity or becomes serious during or after the time of Visit 6 IMP infusion. For patients that were in the Placebo-Controlled Period when recruitment was stopped, a TEAE that starts or increases in intensity or becomes serious at or after the date of the Week 4 Visit.

If an adverse event starts on the day of the Visit 6 IMP infusion, but with an unknown start time, the adverse event will be classified as treatment-emergent in the placebo-controlled period.

14.1.5 Presentation of Adverse Events

All adverse events will be listed for the APRS, including a flag for TEAEs.

Unless otherwise specified, adverse events will be reported for the Placebo-controlled Period for APTS and for the Delayed Start Period for APTS_DS.

For the Placebo-controlled Period and the Delayed Start Period, an overview of the percentages of patients with TEAEs, TEAEs leading to infusion interruption, serious adverse events (SAEs), or adverse events leading to withdrawal, and of patients who died will be provided. For TEAEs, SAEs, and adverse events leading to withdrawal, and TEAEs leading to infusion interruption the total number of events will be included.

14.1.6 Presentation of Pre-treatment Adverse Events

Pre-treatment adverse events will be summarized by preferred term for the APTS.

14.1.7 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided by period:
- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs by sex and preferred term
- TEAEs with an incidence ≥2% [in any treatment] 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 V3 for the Placebo-controlled Period and day of V6 for the Delayed Start Period)

14.1.8 Presentation of Deaths

All the adverse events in patients who died will be listed for the APRS.

14.1.9 Presentation of Serious Adverse Events

All the SAEs will be listed for the APRS.

Treatment-emergent SAEs will be summarized by:
- SOC and preferred term
- preferred term

14.1.10 Presentation of Adverse Events Leading to Withdrawal

All the adverse events leading to withdrawal will be listed for the APRS.

TEAEs leading to withdrawal will be summarized by:
- SOC and preferred term
- preferred term

14.1.11 Presentation of Adverse Events Leading to Study Drug Infusion Interruption

All AEs leading to study drug infusion interruption will be listed for the APRS.

TEAEs leading to study drug infusion interruption will be summarized for the Placebo-controlled Period and for the Delayed Start Period by SOC and preferred term.

14.1.12 Presentation of 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 5.

The following summaries of treatment-emergent AESIs will be provided for the Placebo-controlled Period and for the Delayed Start Period:
- AESIs by SOC and preferred term
- AESIs by SOC and preferred term, separately for each individual event category

14.2 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 based on the APTS_DS for the Delayed Start Period.

For the Placebo-controlled Period, descriptive statistics for the safety variables, both absolute values and changes from baseline (Visit 3) will be presented by visit.

For the Delayed Start Period, descriptive statistics for the safety variables, both absolute values and changes from Baseline (Visit 3 at Week 0), will be presented by visit.

The number and percentage of patients with at least one PCS value at any post-baseline assessment time point will be summarized by variable for the Placebo-controlled Period and for the Delayed Start Period. All available assessments will be included in the evaluation of PCS values. PCS assessments for the Delayed Start Period will use the start of the Placebo-controlled Period as Baseline for parameters where the PCS criteria involves a change from Baseline.

For patients with post-baseline PCS values, listings will be provided including all the values for those patients for the variable by treatment period, with flagging of PCS values.

For parameters where the PCS decision is based upon a comparison with baseline, the visit 3 will be used as baseline.

14.3 Clinical Safety Laboratory Test Data

14.3.1 Data Presentation

The PCS criteria used for the clinical safety laboratory are the Lundbeck standard PCS criteria described in SOP_09978: *GPV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 1.

The clinical safety laboratory test values will be presented in both conventional and Système International (SI) units.

For urine dipsticks, for which the results are categorical values (for example, negative, trace, 1+, 2+), the number and percentage of patients will be summarised for each test by visit.

The microscopy results will be listed for patients with findings by assessment time point.

14.3.2 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[2] using the following criteria:

- ALT or AST >2×, >3×, >5×, >10×, or >20×ULN
- total bilirubin (BILI) >2×ULN
- alkaline phosphatase (ALP) >1.5×ULN
- ALT or AST >3×ULN AND total bilirubin >1.5× or >2×ULN

Patients fulfilling any of the criteria will be listed, and the listing will include all the ALT, AST, BILI, and ALP values for those patients, sorted by assessment date and time in ascending order. If a criterion for a test is fulfilled, the value will be flagged with the highest criterion fulfilled (for example, AST >3×ULN, >5×ULN, >10×ULN, or >20×ULN).

In addition, assessment time points for patients for whom Hy's Law is potentially fulfilled will also be flagged in the listing (pHYL):

- ALT or AST >3×ULN AND
- alkaline phosphatase <2×ULN AND
- total bilirubin ≥2×ULN

The number of patients who met any of the criteria specified above at any post-baseline visit will be summarized by actual treatment and period. In the summaries, each patient will be counted only once using the maximum assessment, or the most severe for the combined criteria. The summaries will also include the number of potential Hy's Law cases.

14.4 Vital Signs and Weight

The PCS criteria used for vital signs and weight are the Lundbeck standard PCS criteria described in SOP_09978: *GPV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 2.

14.5 ECGs

The PCS criteria used for the ECG parameters are the Lundbeck standard PCS criteria described in SOP_09978: *GPV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 3.

In addition to the tables and listings specified in section 14.2, absolute values and changes from Baseline (Visit 3) in QTcF will also be summarized categorically by visit and treatment, separately for the Placebo-controlled Period. The categories that will be used are as follows for the absolute QTcF values:

- QTcF interval < 450 msec
- QTcF interval 450 - 480 msec
- QTcF interval > 480 - 500 msec
- QTcF interval > 500 msec

The categories that will be used for the change from baseline QTcF values are:

- QTcF interval increase from baseline > 30 msec
- QTcF interval increase from baseline > 60 msec

Furthermore, the number and percentage of patients being classified as having either a normal, abnormal but not clinically significant, abnormal and clinically significant, or not interpretable ECG result based on the overall interpretation of the ECG from the investigator will be summarized by visit and treatment, separately for each period.

14.6 Other Safety Endpoints

14.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Scores

The C-SSRS was administered:

- for lifetime (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening Visit 2 that collects a lifetime recall
- for the past 1 month at screening (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening Visit 2 that focuses on the last month
- at baseline (using the *Since Last Visit Version*) – the C-SSRS assessment at baseline that collects information since the previous visit
- post-baseline (using the *Since Last Visit Version*) – the C-SSRS assessments after baseline

The numbers and percentages of patients with lifetime, past 1 month, baseline, or post-baseline ideations or behaviours based on the C-SSRS will be summarized by treatment. For each summary, the most severe item with an answer "Yes" for each patient according to the ordering given in Panel 2 is displayed. For the post-baseline assessments, the summaries will be by treatment and period.

The number and percentage of patients with *no suicidal ideation or behaviour* will be included in the summaries.

Panel 2 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)	

Missing C-SSRS scores will not be imputed.

Positive responses to *non-suicidal self-injurious behaviour* will be summarized separately.

For patients with any post-baseline suicidal ideation or behaviour (C-SSRS scores of 1 to 10), listings will be provided including all C-SSRS scores for those patients.

15 Immunogenicity

For subjects with pre-existing antibodies at baseline, the number and percent of subjects who are positive for anti-eptinezumab antibody will be summarized at baseline. The number and percentage of subjects who develop anti-drug antibodies to eptinezumab during the trial will be summarized by visit. Denominators for percentages will be the total number of samples taken for the visit. Patients with neutralizing anti-eptinezumab antibodies will also be summarized by visit.

Subjects with a positive anti-eptinezumab antibody result (ADA, NAb) will be listed together with site, treatment, patient screening number, age, weight, sex, and visit.

Summaries of TEAEs by SOC and preferred term for patients who are ADA-positive will be provided for the period from baseline and until the Safety Follow-up Visit.

In addition, summaries of TEAEs of Hypersensitivity and Anaphylactic Reactions by SOC and preferred term for patients who are ADA-positive will be provided for the period from baseline and until the Safety Follow-up Visit.

Subjects with a positive ADA and adverse events occurring after start of Visit 3 IMP infusion will be listed. The listing will include the ADA result, the assessment date, the preferred term for the adverse event, and start date and stop date of the adverse event. The ADA results and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

If appropriate, data will be summarized or listed for:

- Titer range (median and interquartile range (IQR)) for subjects with pre-existing antibodies at baseline and for subjects that are ADA positive at Week 16
- For subjects with pre-existing antibodies at baseline, the ratio of Week 16 titer to the baseline titer
- Mean exposure for subject that are ADA-positive at Week 16

All immunogenicity data will be listed by subject and period.

16 Pharmacokinetic/Pharmacodynamic Analyses

A separate analysis plan for pharmacokinetic/pharmacodynamic analyses will be prepared by Quantitative Pharmacology, H. Lundbeck A/S. The PK/PD analysis plan will be finalized before unblinding/data delivery of plasma concentrations.

17 Blinded Data Reviews

The quality of the study will be overseen by performing blinded data reviews during the conduct of the study. The reviews may include, but are not limited to, data quality, protocol

adherence, and the appropriateness of design assumptions, including the sample size assumptions.

18 Interim Analyses

An interim futility analysis will be performed based on 204 randomized and treated patients who have had the chance of completing the Week 4/Visit 6, to allow for stopping the study for futility if the level of efficacy is considerably lower than expected. If the estimated treatment effect for the primary endpoint is less than 1/3 of the expected effect size (3.00/3 = 1) Lundbeck may decide to stop the study for futility.

When the patients have had the chance of having the Week 4 visit (Visit 6), the data will be cleaned and send to an independent CRO (Biostata) as well as treatment codes and the independent CRO will unblind the data and perform the interim analysis. Lundbeck and the CRO conducting the study will remain blinded.

The interim analysis will be based on the primary analysis performed by the independent CRO, analysing the change from Baseline in the number of weekly attacks (Weeks 1-2).

The independent CRO will inform a predefined group of Lundbeck employees whether the criterion for the interim futility have been met or not (this will be described more thoroughly in an Interim Charter). No further details of the interim analysis results will be provided to Lundbeck. Lundbeck may decide to stop the study for futility or continue the enrolment. Recruitment continues while the interim analysis is conducted.

Details of the statistical analysis for the interim analysis will be described in an Interim Statistical Analysis Plan.

19 Sample Size Considerations

Goadsby (2019)[3] describes a study in eCH, where the first 4 weeks have a design similar to this study. The difference between galcanezumab and placebo in change from baseline in weekly frequency of attacks at Week 1 is estimated at -1.5 attacks, and at Week 2 is estimated at -4.4 attacks. The average difference to placebo across Week 1 and Week 2 is estimated at -3.0. Based on the CI presented in the publication, the SD at Week 1 is estimated at 9.2 and the SD at Week 2 is estimated at 11.1. Assuming that the correlation between Week 1 and Week 2 is 0.56, the SD for the average of Week 1 and 2 will be SD = 9.0.

Assuming a difference of eptinezumab to placebo of -3.0 attacks with an SD = 9.0, 144 patients per treatment will provide 80% power for seeing an effect using a two-sided 5.0% significance level.

Since the estimated treatment difference may be slightly decreased due to the use of pMI, an additional 5% of patients have been added. This yields a total of 152 patient per treatment sequence.

20 Statistical Software

The statistical software used will be SAS®, Version 9.4 or later.

21 Changes to Analyses Specified in the Protocol

NA

22 Changes compared to version 1 of the SAP

After the interim result and the data base release and headline results for the Placebo-controlled Period were available, the SAP has been updated to reflect the following changes:

- For patients that were in the Placebo-controlled Period when recruitment was stopped, it has been clarified how they were assigned to the Delayed Start period, since it was not possible to use the timing of the second infusion of IMP as the delimiter between Placebo-controlled and Delayed Start Periods for these patients.
- For the key secondary endpoint "Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks)", it has been clarified how to calculate the time for censored observations.
- The all-patients-treated in Delayed Start Period set (APTS_DS) has been added to clarify what patients are included in the safety analyses for the Delayed Start Period.

Panel 3 Changes to the SAP from Edition 1.0 to 2.0

Section Number	Section Title	Change / Rationale for Change
2 3.2 3.3 3.4 10 14.1.4	Study Design Definition of Periods Definition of Withdrawal Definition of Planned versus Actual Treatment Recent and Concomitant Medication Allocation of TEAEs to Treatment Periods	*Added*: Text has been added in all these sections to clarify how to address patients that were in the Placebo-controlled Period when it was decided to stop recruitment
13.4.1.3	Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks)	*Added*: Text has been added to clarify how to calculate the time when resolution was not obtained

Section Number	Section Title	Change / Rationale for Change
6 8.1 14.1.5 14.1.7 14.1.9 14.1.11 14.1.12 14.2	Analysis Sets Summary of Patient Disposition Presentation of Adverse Events Presentation of Treatment Emergent Adverse Events Presentation of Serious Adverse Events Presentation of Adverse Events Leading to Study Drug Infusion Interruption Presentation of Adverse Events of Special Interest General Methodology for Other Safety Data	*Added/Updated*: Text has been added to describe the APTS_DS data set and updated to clarify when this data set will be applied
14.2	General Methodology for Other Safety Data	*Updated:* It has been clarified that all changes will be seen in comparison to Baseline (Week 0).

23 Details on Data Handling

23.1 Derived Variables

23.1.1 eDiary

The data based on the eDiary will be summarised weekly. The post-baseline weekly intervals start with the day after the first infusion (Day 1) and then count Day 1 to Day 7 as the first week and continue with 7-day weeks from there.

Days where the eDiary is completed, are days where at least one cluster headache were recorded in the cluster headache eDiary or it was confirmed in the evening eDiary that no cluster headaches had taken place during that day.

In case of a reporting day where a patient answers in the evening diary that they experienced a cluster headache on that day but the patient never records an actual cluster headache in the cluster headache eDiary, the day will be assigned as day where the eDiary has not been completed and imputation rules as specified below will be applied.

23.1.1.1 Imputation of missing baseline assessments

The baseline assessments use the eDiary data collected in the Screening Period 2. In case of extension of Screening Period 2, the baseline assessments will be based on the first 7 days in the extension of Screening Period 2, and with no extension of Screening Period 2 the baseline assessments will be based on the first 7 days in screening period 2. If the eDiary is completed on at least 4 out of the 7 days, the baseline assessments will be calculated using pro-rating.

The baseline number of weekly attacks will be calculated as follows:

7(Reported number of attacks/Reported eDiary Days)*

For patients with ≤3 days with observations during the Baseline Period, the missing baseline number of weekly attacks will be drawn from a normal distribution with the mean and SD taken from the baseline number of weekly attacks for patients where a baseline number of weekly attacks has been obtained (from patients with at least 4 of 7 days of observations and possibly using prorating for the calculation). If needed, this step will be incorporated as the initial step of the pMI analysis, and thus new random baseline values will be drawn for each of the 200 simulated data sets, in case of missing baseline values.

For the endpoint Change from Baseline in number of Daily attacks (Days 1-3), the baseline number of daily attacks will be calculated as baseline number of weekly attacks divided by 7.

23.1.1.2 Imputation of missing post-baseline eDiary assessments

For 7-day weekly periods where the eDiary is completed on at least 4 out of the 7 days, prorating will be used, where days with missing information are imputed by the observed mean number of attacks in the 7-day week as follows:

7(Reported number of attacks/Reported eDiary Days)*

For 7-day weekly periods where the eDiary is completed on 3 days or less the 7-day weekly observation will be set to missing.

For similar endpoints, based on information from the eDiary (Cluster headache and evening eDiary) combined into 7-day weekly periods, prorating as described above will be used when the eDiary has been completed for at least 4 days, and the weekly observation will be set to missing, when the eDiary has been completed for 3 days or less.

The number of daily attacks (Days 1-3) will be calculated as follows if the eDairy has been completed for at least 2 of the 3 days (Day 1, Day 2, and Day 3):

Reported number of attacks/Reported eDiary Days

For number of attacks starting within 24 hours of the start of the first infusion, no imputation of data will be done, and the endpoint will only be calculated if there are data available from both the day of infusion and the day after infusion.

23.1.1.3 Imputation for sensitivity analysis assessing the impact of use of transitional medication for eCH

To reflect the set of strategies used for the sensitivity analysis, data collected on the days after use of transitional medication (GON block and oral steroids) will not be used for this analysis when generating the weekly scores.

For the data remaining after removal of data in the PBO-controlled Period following transitional medication (GON block and oral steroids), periods where the eDiary is completed on at least 4 out of the 7 days will be prorated by imputing by the observed mean number of attacks in the period as follows:

7(Reported number of attacks/Reported eDiary Days)*

23.1.1.4 Responder Rates

The following responder rates will be derived: 30%, 50%, and 75%. A responder is a patient, who achieves a ≥30% reduction, ≥50% reduction, or ≥75% reduction from Baseline in weekly number of attacks at a certain week, compared to the baseline weekly number of attacks. The derivation of these responder endpoints will be based on the weekly number of attacks resulting from the imputations described in section 23.1.1.2.

For response across more than one weekly period, the average of the change from baseline for each weekly period is calculated and divided by the baseline value and the result used to determine the response across the weekly periods. As an example, the ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2) is calculated as follows:

Response = 1, if

(Change from baseline in the number of weekly attacks (Week 1)

+

Change from baseline in the number of weekly attacks (Week 2))

/(2 x Baseline number of weekly attacks)

<= -0.5, else Response = 0.

If one or more weekly score is missing for a patient, the average of the existing scores for that patient are calculated within the specified interval and used for calculation of response. If all weekly scores are missing, then the response will be set to non-response.

23.1.1.5 Time from first infusion of eptinezumab to resolution of cluster headache bout (within the first 4 weeks and 16 weeks)

The endpoint: Time from first infusion of eptinezumab to resolution of cluster headache bout (within the first 16 weeks) is only defined and calculated for patients randomized to eptinezumab at Baseline.

Resolution is defined as the day after the last day with cluster headache attacks of moderate or severe pain or where abortive medication (triptans or O2) was used (whichever is the latest), when this is followed by a 2-week period free of cluster headache attacks or with cluster headache attacks with only mild pain, not requiring the use of abortive medication, where

both weeks in the 2-week period had at least 4 days of eDiary compliance. Should this happen more than once, it will be the first instance that counts as resolution. The 2-week period free of attacks or with only mild pain are allowed to start on any day within the period, and not confined to Day 1, Day 8 etc. Since the eDiary is only measured until Week 16, resolution can only happen between Day 1 and Week 14, since it needs to be followed by two weeks of eDiary data that fulfils the criteria mentioned above.

23.1.2 Patient Global Impression of Change (PGIC)

The PGIC is a single patient-reported item reflecting the patient's impression of change in their disease status since the Baseline Visit (Day 0/Visit 3) (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 from 1 (very much improved) to 7 (very much worse).

23.1.3 Sleep Impact Scale (SIS)

The SIS[4] is a patient-reported scale to assess quality of life resulting from sleep disturbance. The SIS questionnaire includes 35 items belonging to 7 domains to assess sleep impact: daily activities (5 items); emotional well-being (4 items); emotional impact (4 items); energy/fatigue (5 items); social well-being (6 items); mental fatigue (3 items); and satisfaction with sleep (8 items). Each item, for 6 out of the 7 domains, is rated on a 5-point scale ranging from 1 ("always" or "all of the time") to 5 ("never" or "none of the time"), whereas satisfaction with sleep is rated on a 5-point scale ranging from 1 (very satisfied) to 5 (very dissatisfied). Each domain yields a score ranging from 0-100.

Items within each domain were summed and transformed to a 0–100 scale using the formula [(Σ items – # of items)/ range] * 100.

A higher score indicated better quality of life (reverse scoring for the satisfaction with sleep domain).

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

The EQ-5D-5L[5] is a patient-reported assessment designed to measure the patient'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). The VAS ranges from 0 (*worst imaginable health state*) to 100 (*best imaginable health state*). The respondents rate their overall health on the day of the interview on a 0–100 hash-marked, vertical visual analogue scale.

23.1.5 Health Care Resource Utilization (HCRU)

Cluster headache-specific healthcare resource utilization information will be collected in terms of outpatient health care professional visits, emergency room visits, hospital admissions, as well as duration of hospital stays during the past 4 weeks. Clinical site personnel and patients will be instructed to capture utilization that takes place outside of visits associated with their participation in the clinical trial.

23.1.6 Work Productivity and Activity Impairment: General Health version 2 (WPAI:GH2.0)

The WPAI:GH2.0[6] is a patient self-rated scale designed to provide a quantitative measure of the work productivity and activity impairment due to a health condition. The WPAI:GH2.0 assess activities over the preceding 7 days and consists of 6 items: 1 item to assess whether the patient has a paid job, 3 items assess the number of hours worked, the number of hours missed from work due to the patient's condition, or due to other reasons, and 2 visual numerical scales assess how much the patient's condition affects their productivity at work and their ability to complete normal daily activities.

The derivation of the WPAI:GH2.0 sub-scores[7] is given in Panel 4, where Q1-Q6 refers to question 1-6 in the questionnaire.

Panel 4 Derivation of WPAI:GH2.0 sub-scores

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

If the answer to Q1 (Are you currently employed (working for pay)?) is 'Yes' but Q2 (During the past seven days, how many hours did you miss from work because of your health problems?) and Q4 (During the past seven days, how many hours did you actually work?) are both 0, then the derived scores for Absenteeism and Work productivity score will be set to missing.

23.2 Assigning Data to Visits

23.2.1 Rating Scales

Panel 5 Windowing rules for scales

Only assessments at withdrawal visits or unscheduled visits will be windowed.

	HCRU WPAI	PGIC	EQ-5D	SIS	Day
Day, PBO-controlled Period					
					0
		1 to 10			7
		11 to 21	1 to 21	1 to 21	14
	2 to 28	22 to 28	22 to 28	22 to 28	28
Day, Delayed Start period					
	29 to 70	29 to 84	29 to 84	29 to 70	56
	71 to 98			71 to 98	84
	>98	>84	>84	>98	112

As withdrawal visits can occur in the Delayed Start Period, the windowing is also applied in this period even though some scales do not have nominal visits in the period.

If there are competing visits the value that will be used in summary tables by visit will be the one that prioritizes values from withdrawal visits above values from nominal and then unscheduled visits.

In the ordering of multiple assessments per visit, assessments will be ordered by recorded time, and assessments without recorded time will come before assessments with recorded time and the last in the ordering will be picked.

For scales assessed after IMP-infusion (but should have been assessed prior to IMP-infusion), the assessment will be assigned to the time point where it should have been assessed. That includes the baseline period as well.

These events will be discussed, and decisions documented in classification meeting.

For eDiary data, the periods will be defined by the assessments according the number of planned days from first IMP-infusion.

23.2.2 eDiary

All eDiary assessments used in endpoints analysing assessments per week are windowed using the planned days: 7, 14, 28 etc.

23.2.3 Safety Variables

Panel 6 Windowing rules for Lab and ECG assessments

	Lab	ECG	Day
Day, PBO-controlled Period			
	≤0	≤0	0
	1 to 28	1 to 28	28
Day, Active treatment period			
	29 to 140	29 to 140	112
	>140	>140	168

Panel 7 Windowing rules for VS/body assessments

	VS/body	Day
Day, PBO-controlled Period		
	NA	Screening
	NA	0 pre-dose
	post-dose to Day 14	0 post-dose
	>14 and < 2nd IMP infusion	28 pre-dose
Day, Delayed Start Period		
	>=2nd IMP infusion and < =70	28 post-dose
	>70 and <=140	112
	>140	168

If there are competing visits the value that will be used in summary tables by visit will be the one that prioritizes values from nominal visits above values from withdrawal or unscheduled visits that is closest to the nominal visit.

In the ordering of multiple assessments per visit, assessments will be ordered by recorded time, and assessments without recorded time will come before assessments with recorded time and the last in the ordering will be picked.

Vital Signs pre-dose at baseline will be assigned the baseline period.

In general, lab, VS, and ECG will be assigned periods according to the IMP-infusions.

23.3 Handling Missing or Incomplete Dates/Times

23.3.1 Withdrawal Date

Missing withdrawal dates will not be imputed and time to withdrawal from study will not be calculated for missing withdrawal dates.

23.3.2 IMP Start and Stop time points

No imputations will be done if IMP start and/or end time point is missing.

23.3.3 Medical Disorder Start and Stop Dates

Incomplete dates will not be imputed. Classification of events into *concurrent medical disorders* or *past disorders* will be based on the reported ongoing status.

23.3.4 Medication Start and Stop Dates

Imputation of incomplete or partially missing dates will be performed in order to document the assigned categories specified in chapter 10.

The algorithm for imputing the start dates will follow the one used for imputing adverse event start dates, see section 23.3.5. If (partly) missing start dates occur, they will only be imputed for summarizing the use of concomitant medication, not for the sensitivity analysis for the primary endpoint.

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 Delayed Start Period), depending on the (possibly imputed) start date, i.e. if the start date is at or after the date of V6 IMP infusion, the medication is only considered ongoing in the Delayed Start Period. If no information at all is provided, then medication is considered ongoing in both periods.

23.3.5 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 and assignment of the adverse event to a period. 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.

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

Patients with no IMP infusion

For patients 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 that have been treated

For patients, 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 first dose of IMP
  - 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.

23.4 Treatment-emergent AEs

Event	Treatment-emergent (Yes/No)
AE starts at or after first dose of IMP	Yes
Change in intensity	- If prior to first IMP => No - If at or after first IMP **AND** intensity increase => Yes - If at or after first IMP **AND** intensity decrease => No
AE becomes SAE	- If prior to first IMP => No - If at or after first IMP => Yes
Events that happen simultaneously: SAE and change in intensity	- If prior to first IMP => No - If at or after first IMP => Yes (due to SAE, regardless of the direction of the intensity change)

23.5 Data with Multiple Records

23.5.1 Dose Changes in Medication Events

Dose changes in medications are recorded on multiple rows in the dataset, with different start and stop dates. When classifying medications into categories (see chapter 10), each dose is considered a separate medication, and the same medication can be assigned to several categories for the same participant. Within a category, multiple entries contribute as a single count.

23.5.2 Changes in Intensity or Seriousness of Adverse Events

An adverse event that changes in intensity in a period will contribute to the count of events as a single event.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used. The maximum intensity is searched for in events with changes, as well as over repeated events based on the preferred term. Adverse events for which information on intensity is missing will be classified as *severe*.

Adverse events with an update in seriousness will be included in ADaM with a new row. For such an event, the start date of the serious adverse event will be set to the start date of the change of seriousness. This means that an adverse event with a start date prior to first infusion of IMP (i.e. not classified as treatment-emergent) that is registered as serious after first IMP infusion will be classified as treatment-emergent.

Adverse events for which information on seriousness is missing will be classified as *serious*.

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Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Study title:	Interventional, randomized, double-blind, parallel-group, placebo-controlled delayed-start study to evaluate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache
Study No.:	19386A
SAP date:	12 October 2023

This document has been signed electronically. The signatories are listed below.

Authentication

PPD

PPD

PPD

PPD

Authorization

PPD

PPD

Appendix II

SAS® Code

SAS® Code

PRIMARY ANALYSIS

Key elements of the pMI analysis:

```
* Step1: Create a number of data sets, where MCMC is used to make
all data sets monotone missing;

proc sort data=adam.adeffch (where=(RANDFL='Y' and
paramcd='ATTACKW')) out=adeffch;
   by usubjid trt01p base AVISITN;
run;

proc transpose data = adeffch out = adeffch_mi (drop = _NAME_
_LABEL_) prefix = AVISITN_;
    by USUBJID TRT01P BASE COUNTRY;
    var CHG;
    id AVISITN;
run;

proc sort data=adeffch_mi;
   by trt01p;
run;

proc mi data = adeffch_mi out = Org_im nimpute = 200 seed = 210876;
   by trt01p;
      var base avisitn_1 avisitn_2 avisitn_3 avisitn_4;
   mcmc chain = multiple
      impute = monotone;
run;

* Step 2: Impute missing values within specified class variables;
* Use placebo mean imputation by using the placebo variables to im-
pute from;
proc sort data = Org_im;
   by _IMPUTATION_;
run;

proc mi data = Org_im seed = 67653179 nimpute = 1 out = Org_im2;
   by _IMPUTATION_;
   class trt01p;
   monotone regression;
   mnar model(avisitn_1 avisitn_2 avisitn_3 avisitn_4/ modelobs =
(trt01p = 'PBO'));
   var base avisitn_1 avisitn_2 avisitn_3 avisitn_4;
```

```
run;

* Transform back to vertical structure;

proc sort data = Org_im2;
   by _IMPUTATION_ usubjid;
run;

proc transpose data = Org_im2 out = MI (rename=(COL1=CHG
_NAME_=AVISIT));
   by _IMPUTATION_ USUBJID BASE TRT01P COUNTRY;
   var avisitn_1 avisitn_2 avisitn_3 avisitn_4;
run;

proc sort data=MI out=MI_final;
   by _IMPUTATION_;
run;

proc mixed noclprint data= MI_final ic method=reml;
   by _IMPUTATION_;
   class usubjid country (ref='xxx') trt01p avisit;
   model chg = base*avisit country trt01p*avisit /s ddfm=kr;
   repeated avisit /subject=usubjid type=UN;
   lsmeans trt01p*avisit / diff cl;
   estimate 'EPTI 400 mg vs PBO Week 1-2' trt01p*avisit 1 1 0 0
      -1 -1 0 0/ divisor=2;
   ods output estimates=est_chg_MI;
run;

proc mianalyze data = est_chg_MI;
   modeleffects Estimate;
   stderr StdErr;
   ods output ParameterEstimates = param_est;
run;
```

For patients with ≤3 days with observations during the Baseline Period:

```
*Create 200 random baselines based on baseline mean and SD from all
patients;

data random_baselines;
   seed =38264387;
   do obs = 1 to 200;
   baseline_random = rand ('normal',mean,SD);
   output;
   end;
run;

*Create i=1 to 200 random seeds for the monotone procedure;

data random_seeds;
```

```
   call streaminit(884);
   do i = 1 to 200;
   random_seed = rand("integer", 1000000, 2000000);
   output;
   end;
run;

* create i=1 to 200 data sets (one for each random seed from above)
using the baseline_random simulated above: one baseline per data
set;

For i=1 to 200;

proc mi data = xxx_i out = yyy nimpute = 1 seed = i;
   by trt01p;
      var baseline_random avisitn_1 avisitn_2 avisitn_3 avisitn_4;
   mcmc chain = multiple
      impute = monotone;
run;

* Now there are simulated 200 data sets, and the procedure of imput-
ing missing values and estimate the treatment effect is the same as
for the primary analysis shown in the beginning of this appendix;
```

KEY SECONDARY ANALYSIS

Response

```
proc logistic data = xyz;
   by week;
   class treatment(ref = "PBO") region / param = GLM;
   model RESPONSE(event = "1") = base region treatment /
      clodds = PL alpha = 0.05;
run;
```

Time from infusion to resolution

```
proc phreg data = xyz;
   class treatment duration;
   model TIME * STATUS(0) = base treatment duration/ ties = EFRON;
      hazardratio treatment / cl = pl;
run;
```

Appendix III
PCS Criteria

PCS Criteria

Table 1 PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
Haematology / Coagulation				
B-haemoglobin	HGB	g/L	≤ 95 (women) ≤ 115 (men)	≥ 165 (women) ≥ 185 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women) ≤ 3.8 (men)	≥ 6.0 (women) ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women) ≤ 0.37 (men)	≥ 0.50 (women) ≥ 0.55 (men)
B-MCV (mean cell volume)	MCV	fL	≤ 0.8 x LLN	≥ 1.2 x ULN
B-total leucocyte (white cell count)	WBC	x 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%		≥ 10
B-basophils/leucocytes	BASOLE	%		≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75
B-monocytes/leucocytes	MONOLE	%		≥ 15
B-thrombocytes (platelet count)	PLAT	x 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio		≥ 2.0
B-prothrombin time	PT	Sec		≥ 18
Liver				
S-aspartate aminotransferase	AST	I/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	I/L		≥ 3 × ULN
S-bilirubin	BILI	µmol/L		≥ 34
S-bilirubin, direct	BILDIR	µmol/L		≥ 12
S-bilirubin, indirect	BILIND	µmol/L		≥ 22
S-alkaline phosphatase	ALP	I/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	I/L		≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L		≥ 20
Kidney				
S-creatinine	CREAT	µmol/L		≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L		≥ 11
S-uric acid (urate)	URATE	µmol/L		≥ 510 (women) ≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL	mmol/L	≤ 90	≥ 117
S-magnesium	MG	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic)	PHOS	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate	BICARB	mmol/L	≤ 12	≥ 38
Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	Hb fract.		≥ 6.5
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	
Cardiac/Skeletal/Muscle				
S-creatine kinase (total)	CK	I/L		≥ 400 (women) ≥ 750 (men)
S-creatine kinase MB isoenzyme	CKMB	µg/L		≥ 8.5 or
	CKMBCK	%		≥ 3.5% of total CK
S-lactate dehydrogenase (total)	LDH	IU/L		≥ 750
S-troponin I	TROPONI	µg/L		≥ 1.5
S-troponin T	TROPONT	µg/L		≥ 0.4
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
S-globulin (total)	GLOBUL	g/L	≤ 15	≥ 55

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
Urine				
Urinary pH	PH		≤ 4	≥ 9

S=serum; B=whole blood; U=urine

Table 2 PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Variable	CDISC Term	Unit	PCS Low	PCS High
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
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
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperature	TEMP	ºC	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value.

Table 3 PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS Low	PCS High
Absolute Time Interval				
PR interval	PRMEAN	Msec		≥ 260
QRS interval	QRSDUR	Msec		≥ 150
QT interval	QTMEAN	Msec		≥ 500
Derived Time Interval				
Heart rate	HRMEAN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCB	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCF	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value.

Appendix IV
Study flow chart

Study flow chart

Table 4 Study Procedures and Assessments

Visit/Period Name	Screening		Placebo-controlled Period					Post-Treatment Observational Period			
	Screening Period 1	**Screening Period 2**	**Baseline Visit**		**Primary Outcome Visit**		**Active Treatment Period**		**Completion Visit**	**SFU Visit [c]**	**Withdrawal Visit[d]**
Visit Number	**1[a, gg]**	**2[a]**	**3[a]**	**4[b]**	**5[b]**	**6[a]**	**7[b]**	**8[b]**	**9[a]**	**10[a]**	**WD[a]**
Day/ End of Week	-371 to -7/ **-53 to -1**	-7 to -1	0/ **0**	7/ 1	14/ **2**	28/ **4**	56/ **8**	84/ **12**	112/ **16**	168 **/24**	
Visit Window[e] (days relative to nominal visit)	**±/1**			**±1**	**±1**	**±1**	**±/5**	**±/5**	**±/5**	**±/5**	
Screening and Baseline Procedures and Assessments											
Signed informed consent(s)	√[f]	√[g]									
Demographics (age, sex, race)	√										
Diagnosis	√	√									
Disease-specific history[h]	√										
Relevant history (social, medical, psychiatric, neurological)	√	√									
Previous cluster headache abortive and preventive therapy use[h]	√	√									
Recent medication (past 3 months prior to the Screening Visit 1/ Screening Visit 2)	√	√									
Substance Use (e.g. smoking & alcohol)	√	√									
Height	√										
Family history of cluster headache	√										
Urine drug screen		√									
Inclusion/exclusion criteria[i]	√	√	√								

Visit/Period Name	Screening		Placebo-controlled Period					Post-Treatment Observational Period			
	Screening Period 1	**Screening Period 2**	**Baseline Visit**		**Primary Outcome Visit**		**Active Treatment Period**		**Completion Visit**	**SFU Visit [c]**	**Withdrawal Visit[d]**
Visit Number	**1[a, gg]**	**2[a]**	**3[a]**	**4[b]**	**5[b]**	**6[a]**	**7[b]**	**8[b]**	**9[a]**	**10[a]**	**WD[a]**
Day/ End of Week	-371 to -7/ **-53 to -1**	-7 to -1	0/ **0**	7/ 1	14/ **2**	28/ **4**	56/ **8**	84/ **12**	112/ **16**	168 **/24**	
Visit Window[e] (days relative to nominal visit)	**±/1**			**±1**	**±1**	**±1**	**±/5**	**±/5**	**±/5**	**±/5**	
Signs and symptoms present at Screening Visit 2 and Baseline Visit (before IMP administration) - recorded on an *Adverse Event Form[hh]*		√	√								
Randomization			√								
Efficacy Assessments (ePROs) [j,k]											
eDiary daily recording[l]		√	√[m]	√	√	√[m]	√	√	√		
eDiary compliance check[n]			√	√	√	√	√	√	√		√
PGIC				√	√	√[m]	√		√		√
SIS			√[m]		√	√[m]					√
Pharmacoeconomic Assessments (ePROs)											
EQ-5D-5L			√[m]		√	√[m]	√		√		√
HCRU[j]			√[m]			√[m]					
WPAI:GH2.0[j]			√[m]			√[m]					
Pharmacokinetic Assessments											
Blood sampling for IMP quantification			√[o]			√[o]			√	√	√
Pharmacodynamic Assessments											
Blood sampling for exploratory biomarkers			√[o]			√[o]			√	√	√
Safety Assessments											
Adverse events		√[hh]	√[p,q,r]	√	√	√[p,q,r]	√	√	√	√	√
Blood and urine sampling for clinical safety laboratory tests		√	√[q]			√[q]			√	√	√

Visit/Period Name	Screening		Placebo-controlled Period					Post-Treatment Observational Period			
	Screening Period 1	Screening Period 2	Baseline Visit		Primary Outcome Visit		Active Treatment Period		Completion Visit	SFU Visit [c]	Withdrawal Visit[d]
Visit Number	**1**[a, gg]	**2**[a]	**3**[a]	**4**[b]	**5**[b]	**6**[a]	**7**[b]	**8**[b]	**9**[a]	**10**[a]	**WD**[a]
Day/ End of Week	-371 to -7/ **-53 to -1**	-7 to -1	0/ **0**	7/ 1	14/ **2**	28/ **4**	56/ **8**	84/ **12**	112/ **16**	168 **/24**	
Visit Window[e] (days relative to nominal visit)	**±/1**			**±1**	**±1**	**±1**	**±/5**	**±/5**	**±/5**	**±/5**	
Blood sampling for ADA including NAbs			√[q]						√	√	√
Vital signs (including body temperature), weight	√[s]	√	√[q,r]			√[q,r]			√	√	√
ECG		√	√[q]			√[q]			√	√	√
Examinations (physical, neurological)[t]		√	√			√			√	√	√
C-SSRS[u]		√	√[q]			√[q]	√		√	√	√
Biobanking[v]											
Blood sampling for gene expression profiling (RNA)[w]			√			√			√		√
Blood sampling for future exploratory biomarkers[w]			√[o]			√[o]			√		
Blood sampling for metabolomics/proteomics (plasma)[w]			√			√			√		√
Blood sampling for pharmacogenetics (DNA) (optional)[x]			√								
Blood sampling for possible future ADA assessment[w,y]			√[z]						√	√	√
Other Study Procedures and Assessments											
IMP administered (IV infusion)[aa]			√[bb]			√[bb]					
IMP accountability[cc]			√			√					
Concomitant medication (prescription and non-prescription)		√	√[q]	√	√	√[q]	√	√	√	√	√

Visit/Period Name	Screening		Placebo-controlled Period					Post-Treatment Observational Period			
	Screening Period 1	Screening Period 2	Baseline Visit		Primary Outcome Visit		Active Treatment Period		Completion Visit	SFU Visit [c]	Withdrawal Visit[d]
Visit Number	**1**[a, gg]	**2**[a]	**3**[a]	**4**[b]	**5**[b]	**6**[a]	**7**[b]	**8**[b]	**9**[a]	**10**[a]	**WD**[a]
Day/ End of Week	-371 to -7/ **-53 to -1**	-7 to -1	0/ **0**	7/ 1	14/ **2**	28/ **4**	56/ **8**	84/ **12**	112/ **16**	168 **/24**	
Visit Window[e] (days relative to nominal visit)	**±/1**			**±1**	**±1**	**±1**	**±/5**	**±/5**	**±/5**	**±/5**	
eDiary training		√									
ePRO training		√									
eDiary closeout[dd]									√		√
Pregnancy test[ee]	√	√	√[q]			√[q]			√	√	√

ADA = anti-drug antibody; BL = baseline; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L= EuroQol 5-Dimension 5-Level; HCRU = Health Care Resources Utilization; IMP = investigational medicinal product; IV = intravenous; PGIC = Patient Global Impression of Change; ePRO = electronic patient-reported outcome; SAE = serious adverse event; SFU = Safety Follow-up; SIS = Sleep Impact Scale; WD = Withdrawal; WPAI:GH2.0 = Work Productivity Activity Questionnaire: General Health second version

a This visit should be a site visit. The Screening Visit 1 assessments may be extended over several days if needed. The date of the first assessment (except ICF) should be entered in the IRT system as the Visit Date.

b For phone visits, the patient will be contacted for eDiary compliance check, to ensure that the selected assessments have been completed and for collection of relevant information such as AEs and concomitant medications.

c The Safety Follow-Up Visit (SFU), should be scheduled 20 weeks (5 half-lives) after the last IMP administration.

d Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible.

e If the date of a clinic visit or phone contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit (Day 0/Visit 3).

f At Screening Visit 1, the patient will be asked to sign the main Informed Consent Form and the Informed Consent Form for blood sampling for pharmacogenetics (optional). Under exceptional circumstances, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, the discussion with the patients about the Informed Consent Form(s) can be done as a virtual clinic visit and the Informed Consent Form(s) can be provided remotely. Refer to section 4.2.

g At Screening Visit 2, the patient will be asked to confirm consent by re-signing each of the Informed Consent Form(s) signed at Screening Visit 1 (separate signature lines on each form).

h Patients must have adequately documented records or reliable history of episodic cluster headache history and previous treatment for episodic cluster headache within the 12 months prior to Screening Visit 1. See protocol for definition of adequately documented records.

i Patients who meet inclusion criteria 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 15, 18 and none of exclusion criteria 1, 2, 4, 5, 6, 7, 8, 9 (At Screening Visit 1, the investigator must consider excluding patients with a lifetime history of psychosis, bipolar mania, or dementia. Patients with other psychiatric conditions, whose symptoms at Screening Visit 1, are not controlled or who have not been adequately treated must be identified and the investigator should consider initiation of appropriate treatment as medically indicated), 10, 11, 12, 13, 14 (Patients with uncontrolled hypertension at Screening Visit 1, must be identified and the investigator must consider initiation of appropriate treatment as medically indicated), 15, 16, 17, 20, 24, 25, 26, 27, 28, 29 at Screening Visit 1 are eligible to enter Screening Period 1. Patients who meet all of the inclusion and none of the exclusion criteria at the Screening Visit 2 and Baseline Visit (Day 0/Visit 3) are eligible to participate in this study.

j During the Placebo-controlled Period, ePROs which are scheduled in alignment with a clinic visit must be completed in the clinic; ePROs which are scheduled in alignment with a phone contact must be completed in the remote setting on the day of the scheduled phone contact date. During the Active Treatment Period and Post-treatment Observational Period, ePROs which are scheduled in alignment with a clinic visit can be completed in the clinic or in the remote setting within 1 day prior to the scheduled clinic visit date. ePROs which are scheduled in alignment with a phone contact must be completed in the remote setting and can be completed on the day or within 1 day prior to the scheduled phone contact date. HCRU and WPAI:GH2.0 must be administered at site.

k At the Screening Visit 2, the patient must be assisted with the provisioning and training of the eDiary and ePROs. Details will be provided in a separate training module.

l Patients must complete the eDiary from the first day of Screening Period 2 until the Completion Visit (Week 16/Visit 9).

m Patients must complete the daily eDiary and ePRO entries prior to infusion.

n In addition to the eDiary compliance checks performed at the defined clinic visits and phone contacts, ongoing evaluation of eDiary compliance will be performed by the site (based on eDiary reporting) and more frequent contact with patients may be performed in case of non-compliance.

o At IMP visits, two blood samples will be collected for IMP quantification and exploratory biomarkers – one prior to the IMP infusion and one - one hour after the end of the infusion.

p Infusion Related Reactions must be checked as part of the overall AE collection, after infusion and before the patient is discharged from the site.

q Infusion must be preceded by the assessment of vital signs including body temperature, concomitant medications, AEs, ECG, blood sampling (for clinical safety laboratory tests and ADA), urine sampling (for clinical safety laboratory and pregnancy tests) and C-SSRS. Vital signs must be assessed prior to blood sampling.

r Vital signs including body temperature and AEs must be checked after infusion. Vital signs must be assessed prior to blood sampling.

s At Screening Visit 1, only vital signs and weight are assessed. It is recommended to calculate BMI at Screening Visit 1 to assess Exclusion Criterion 9 in preparation for the eligibility assessment of BMI at Screening Visit 2.

t Physical and Neurological examinations for all clinic visits (except Screening Visit 2 which is mandatory) are to be conducted at the discretion of the investigator. If these examinations are conducted at an IMP infusion Visit, these must be performed prior to the infusion.

u C-SSRS will be administered by the authorized rater at the clinic.

v Biobank may be excluded or optional per local regulation.

w Exploratory gene expression profiling (RNA) and metabolomics/proteomics, including blood sampling for possible future ADA assessment and future exploratory biomarkers, is covered by the main Informed Consent Form.

x Sampling for pharmacogenetics is optional and covered by a separate Informed Consent.

y Blood samples for serum separation and possible future ADA analyses will be drawn at Baseline (Day 0/Visit 3), Completion (Week 16/Visit 9), Safety Follow-Up Visit, or the Withdrawal Visit (if the patient withdraws).

z Blood samples for ADA at Baseline (Day 0/Visit 3) will be collected prior to the IMP infusion.

aa 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 study where blinding is necessary.

bb Patients must be monitored during the infusion and for a period of 1 hour from the end-of-infusion. Patients will be requested to stay longer should the investigator or designee determine this is clinically warranted.

cc A designated unblinded CRA is responsible for the IMP accountability.

dd The eDiary closeout will take place at Completion (Week 16/Visit 9) / Withdrawal Visit (for patients who withdraw). Details will be provided in a separate training module.

ee For women of childbearing potential, pregnancy test at Screening Visit 2 and the Safety Follow-up Visit is to be conducted using serum β-HCG. At all other visits, urine pregnancy testing will be performed and in case of a positive finding, further confirmatory testing will be performed via serum β-HCG.

gg For patients who enter the study already in cluster headache bout, Screening Visit 1 and Screening Visit 2 may be combined to capture all assessments for Screening Visit 1 and Screening Visit 2 on the same day.

hh Adverse events (serious and non-serious) must be collected, recorded, and reported to Lundbeck from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

Appendix V
Adverse Events of Special Interest

Adverse Events of Special Interest

Table 5 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 Study 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)	