Statistical Analysis Plan

Interventional, open-label, fixed-dose multiple administration study to evaluate long-term treatment with eptinezumab in participants with chronic cluster headache

Eptinezumab

Trial No.:	19385A
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Table of Contents

Appendices

List of Panels and Tables

List of Abbreviations and Definitions of Terms

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
APES	all-participants-enrolled set
APTS	all-participants-treated set
BMI	body mass index
cCH	Chronic Cluster Headache
CGRP	calcitonin gene-related peptide
CH	Cluster Headache
CI	confidence interval
COA	Clinical outcome assessments
CS	Compound symmetry
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
ePRO	electronic participant-reported outcomes
EQ-5D-5L	Euroqol 5 Dimensions
FAS	Full-analysis set
HCRU	health care resource utilization
IMP	investigational medicinal product
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NAb	Neutralizing antibody
PCS	potentially clinically significant
PGIC	Patient global impression of change
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SE	standard error
SFU	Safety Follow-up
SIS	Sleep Impact Scale
SOC	system organ class
TEAE	treatment-emergent adverse event
WPAI:GH2.0	Work Productivity Activity Impairment: General Health second version

1 Objectives

1.1 Primary Objective

To evaluate the long-term safety and tolerability of eptinezumab in participants with chronic cluster headache (cCH).

1.2 Secondary Objectives

To evaluate the efficacy of eptinezumab in participants with cCH as well as the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity.

1.3 Exploratory Objective

To explore the target engagement of eptinezumab to CGRP.

2 Trial Design

This is an interventional, open-label, fixed-dose multiple administration trial to evaluate the long-term treatment with eptinezumab in participants with cCH.

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

The target population for this trial is defined as participants with cCH, based on the *International Headache Society* International Classification of Headache Disorders third edition (IHS ICHD-3) classification, with documented evidence of cCH prior to screening and confirmed via prospectively-collected information in the eDiary during the Screening Period. A minimum of 14 cluster headache attacks must be captured in the eDiary for the 28-day Screening Period.

The total trial duration from the Screening Visit to the Safety Follow-up (SFU) Visit is approximately 60 weeks and includes Screening Period (4 weeks), Treatment Period (48 weeks), and SFU Period (8 weeks).

Eligible participants will receive four infusions with eptinezumab 400 mg at 12-week intervals at Day 0 (Visit 2), at the end of Weeks 12 (Visit 5), 24 (Visit 8) and 36 (Visit 11), administered as an intravenous (IV) infusion of 45 minutes (+15 minutes).

The SFU Visit will take place at Week 56 (Visit 15); that is, 20 weeks (5 half-lives) after the last eptinezumab administration.

Participants who withdraw from study, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further SFU Visit, scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

Participants who are withdrawn from the treatment will be given the opportunity to remain in the trial at the discretion of the investigator. Participants will be expected to attend all scheduled trial visits and procedures except eptinezumab administration. If participants refuse, they will be asked to attend a Withdrawal Visit as soon as possible and a further SFU Visit, scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

Eligibility will be assessed during the Screening Period and before the first administration of eptinezumab at the Baseline Visit (Day 0/Visit 2).

The following visits will be site visits: Screening Visit at Week -4 (Visit 1), Investigational Medicinal Product (IMP) Visits at Weeks 0, 12, 24 and 36 (Visits 2, 5, 8 and 11), Completion Visit at Week 48 (Visit 14) and SFU Visit at Week 56 (Visit 15) or Withdrawal Visit, if applicable. All other trial visits will be phone contact visits. In exceptional situations to be approved by the Contract Research Organisation's (CRO) medical monitor, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and eptinezumab administration, while the remaining assessments (eDiary, electronic participant-reported outcomes [ePROs], C-SSRS, and investigator evaluations) can be conducted remotely as virtual clinic visits in line with the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) guidance.

Participants will be assigned an eDiary at the beginning of the Screening Period (Visit 1, Week -4) and will be required to complete it:

- Daily - during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40).
- Weekly - for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48.

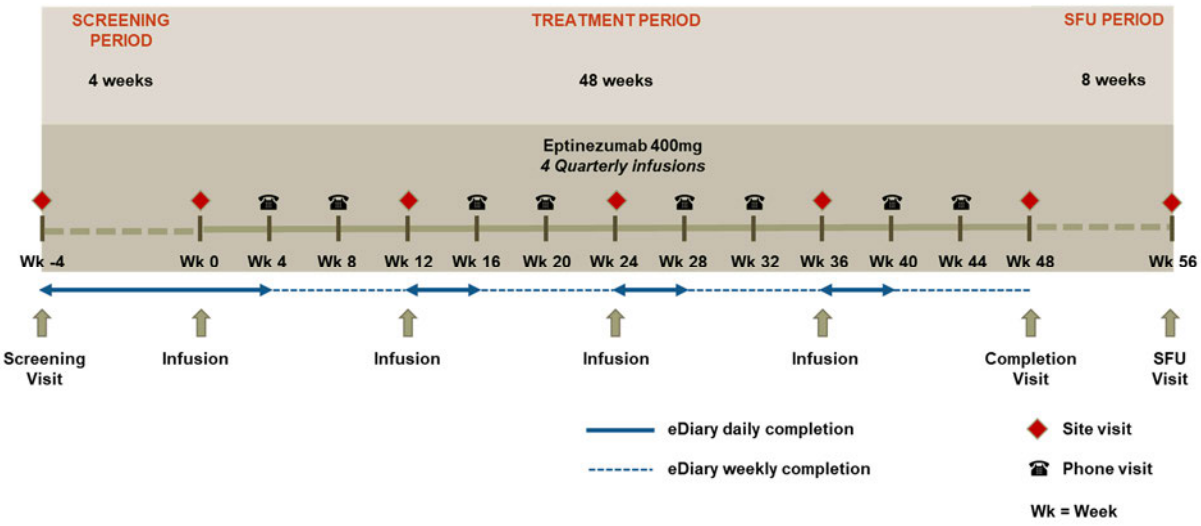
During the trial visits with eptinezumab infusion, eDiary and ePROs must be completed prior to infusion and prior to any interaction with the clinical site staff.

At these visits, safety assessments will be performed before and after the infusion. Safety assessments before eptinezumab infusion consists of vital signs including body temperature, weight, concomitant medications, adverse events, ECG, blood sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, and ADA including NAb), urine sampling (for clinical safety laboratory and pregnancy tests) and C-SSRS. Safety assessments after eptinezumab infusion consists of vital signs including body temperature, and adverse events.

Blood samples for exploratory eptinezumab quantification, and ADA and NAbs assessments will be collected at Weeks 0, 12, 24, 36 and 48 (or at Withdrawal Visit for participants, who withdraw from study) and at SFU Visit (Visit 15). Blood samples for exploratory biomarkers will be collected at Weeks 0, 12, 24, 36 and 48 (or at Withdrawal Visit for participants, who

withdraw from study). ADA and NAbs will be collected before an IMP infusion. Furthermore, at each IMP visit, two blood samples will be collected for exploratory eptinezumab quantification and exploratory biomarkers; one sample prior to the eptinezumab infusion and one sample 1 hour after the end of the infusion.

Panel 1 Trial Design



3 Definitions

3.1 Definition of Baseline

For the efficacy endpoints based on the eDiary, e.g. the number of cluster headache attacks, the data collected during the first 28 days of the Screening Period will be used to calculate the baseline value for the endpoints. In case of a 7-day extension of the Screening Period, the last 21 days of the original 28 days Screening Period and the first 7 days of the extension will be used to calculate the baseline value (if the extension is less than 7 days the days used prior to the extension should be changed accordingly ending up with a total of 28 days). Furthermore, in case of re-screening, the baseline values will be calculated based on the first 28 days of the re-screening period. See section 13.5.1.1.1 and chapter 23 for handling of missing data.

For the endpoints not based on the eDiary, the baseline value is the value captured either during the Screening Visit or at the Baseline Visit prior to the infusion, whichever is later.

3.2 Definition of Periods

The trial consists of the following periods:

- Screening period (4 weeks): Starts at the Screening Visit and continues up to start of IMP infusion at the Baseline Visit

- Treatment period (48 weeks): Starts at the IMP infusion at the Baseline Visit and continues up to and including the Completion Visit
- Safety Follow-up period (8 weeks): Starts after the Completion Visit and continues up to and including the SFU Visit

Unless otherwise specified, the Treatment Period, and the Safety Follow-up Period will be reported as one period.

3.3 Definition of Withdrawal

Based on data captured in the eCRF we define the following categories of withdrawal:
- Withdrawn from treatment
- Withdrawn from study

Participants that do not withdraw from study, will be described as completing the study.

3.4 Definition of a Month

A Month is referring to a 28-day period.

4 COVID-19

For this trial, all participants 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 participants withdrew due to the COVID-19 situation
- Whether participants got diagnosed with COVID-19

Remotely done visits will be tabulated or listed as appropriate. Participants diagnosed or withdrawn due to COVID-19 will be seen from tables/listings of AEs and AEs leading to withdrawal respectively.

5 Endpoints

The endpoints are summarized in Panel 2. There are no key secondary endpoints in this trial.

Panel 2 Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the long-term safety and tolerability of eptinezumab in participants with chronic cluster headache (cCH)	• Primary endpoints: - adverse events - absolute values and changes from Baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values - development of specific anti-eptinezumab antibodies (ADAs) including neutralizing antibodies (NAbs) - Columbia-Suicide Severity Rating Scale (C-SSRS) score
Secondary Objectives • To evaluate the efficacy of eptinezumab in participants with cCH	- Secondary endpoints: - Change from Baseline in the number of weekly attacks (Weeks 1-4 and Weeks 1-2) - Change from Baseline in the number of monthly attacks (Months 1-12) - Conversion from cCH to episodic cluster headache (eCH): no cluster headache attacks for ≥3 consecutive months (≥12 consecutive weeks) (Weeks 1-48) - Change from Baseline in the weekly number of times an abortive therapy (oxygen and/or triptans where it will count as 2 times in case oxygen and triptans were used for the same attack) was used (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Change from Baseline in the weekly number of times an abortive therapy (oxygen) was used (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Change from Baseline in the weekly number of times an abortive therapy (triptans) was used (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Change from Baseline in the number of weekly attacks (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Change from Baseline in the average attack related daily pain (including days with no attacks), as assessed using the 5-point self-rating pain severity scale (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Response: ≥30% reduction from Baseline in the number of weekly attacks (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Response: ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - Response: ≥75% reduction from Baseline in the number of weekly attacks (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) - cCH remission: no cluster headache attacks for ≥1 month (≥4 consecutive weeks) (Weeks 1-48) - cCH remission: no cluster headache attacks for ≥1 month (≥4 consecutive weeks) (Weeks 1-12, 13-24, 25-36, 37-48) - Use of transitional treatment (Weeks 1-48)

Objectives	Endpoints
	- Patient Global Impression of Change (PGIC) score at Weeks 4, 8, …, 48 - Change from Baseline in the Sleep Impact Scale (SIS) domain scores at Weeks 4, 12, 16, 24, 28, 36, 40, 48 - <u>Exploratory endpoints:</u> - Change from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - Change from Baseline in the pain per attack, as assessed using the 5-point self-rating pain severity scale (Months 1, 2, …, 12) - Response: ≥30% reduction from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - Response: ≥50% reduction from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - Response: ≥75% reduction from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - Response: 100% reduction from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - Change from Baseline in the monthly number of times an abortive therapy (oxygen and/or triptans, only oxygen, and only triptans) was used (Months 1, 2, …, 12) - Change from Baseline in the weekly integrated measure of frequency and intensity of attack related pain, that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during a week (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) or the intensity of attack related pain multiplied by the weekly number of attacks (Weeks 5, 6, …, 12, 17, 18, …, 24, 29, 30, …, 36, 41, 42, …, 48) - Use of triptans (Weeks 1-48) - Use of oxygen (Weeks 1-48) - Use of preventive medication (Weeks 1-48) - Sustained response: ≥75% reduction from Baseline in the number of monthly attacks for any month, where all the subsequent months also had ≥75% reduction from Baseline in the number of monthly attacks (Months 1, 2, …, 12) - A maximum score of mild on the 5-point self-rating pain severity scale (Weeks 1, 2, …, 48)
• To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity	- <u>Secondary endpoints:</u> - Change from Baseline in the EuroQol 5-Dimension 5-Level (EQ-5D-5L) score at Weeks 4, 16, 28, 40, and 48 - Health Care Resources Utilization (HCRU) at Baseline and Weeks 4, 16, 28, 40, and 48 - Change from Baseline in the Work Productivity Activity Impairment: General Health second version (WPAI:GH2.0) subscores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Weeks 4, 16, 28, 40, and 48

Objectives	Endpoints
Exploratory Objective • To explore the target engagement of eptinezumab to calcitonin gene-related peptide (CGRP)	• Exploratory endpoint - Change from Baseline in CGRP (CGRP-eptinezumab complex, free CGRP) at Weeks 12, 24, 36, and 48

6 Analysis Sets

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

- *all-participants-enrolled set* (APES) – all enrolled participants
- *all-participants-treated set* (APTS) - all participants in the APES who received infusion with eptinezumab
- *full-analysis set* (FAS) - all participants in the APTS who have a valid assessment of the baseline number of weekly attacks and a post-baseline assessment of number of weekly attacks.

The participants and data will be classified into the analysis sets during a *Classification Meeting* according to the definitions above after the trial database has been released, but prior to the headline results meeting.

Safety analyses (including tolerability and exposure), disposition, demographics and baseline characteristics will be based on APTS.

Efficacy analyses will be based on FAS.

Three Data Point Sets (DPS) will be used for presenting the results using eDiary data:

- DPS1: All data points obtained at or after enrolment
- DPS2: All data points obtained at or after enrolment except for those following the 7-day rule after the use of transitional treatment (for details see section 23.2.4)
- DPS3: All data points obtained at or after enrolment except for those following the 7-day rule after the use of transitional treatment (see section 23.2.4) and those following the 12-week rule after withdrawal from treatment (see section 23.2.1.5)

DPS1 will be used for the descriptive statistics described in chapter 7 as well as the sensitivity analyses described in sections 13.5.9.1 and 13.5.9.2, DPS2 will be used for the short-term efficacy estimand described in section 13.5.1, and DPS3 will be used for the long-term efficacy estimand (section 13.5.3), the sensitivity analysis described in section 13.5.9.3, and analyses based on eDiary data. For more details see chapter 13.

For efficacy data not derived from the eDiary all analyses will be based on all data points obtained at or after enrolment.

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, participant screening number, sex, age, race, and baseline weight.

8 Participant Disposition

8.1 Summary of Participant Disposition

Participant disposition will be summarized overall, and by country, and will include the number of participants in each analysis set defined in chapter 6, and the number of participants in the APTS who

- completed the study
- withdrew from study

To assess the potential impact of COVID-19 on the visit structure, a table will be provided by visit for the visits that are changed from on-site to remote if applicable. The summary will be based on APTS.

8.2 Withdrawals

The number of participants who withdrew from study will be summarized by primary reason for withdrawal and all reasons for withdrawal.

Participants who withdrew from study will be listed and the listing will include the number of days since the first IMP until withdrawal from study, the number of days since the last IMP, and the primary reason for withdrawal, and all reasons for withdrawal.

Kaplan-Meier failure plots of time to withdrawal from study will be presented. The time will be calculated from the date of first dose of IMP to the date of the withdrawal from study or the date of the Completion Visit, whichever comes first. Participants who were in the trial until the Completion Visit or Week 48, whichever comes first, will be regarded as censored from that timepoint.

All tables, graphs, and listings will be based on the APTS.

9 Demographics and Baseline Characteristics

Demographics (sex, age, race, region, country); baseline characteristics (height, weight, and BMI); baseline disease characteristics; and baseline efficacy variables will be summarized.

Baseline disease characteristics comprise of prior preventive medications used, number of treatment failures and reasons for treatment failures for all and by prior preventive medications. Furthermore, family history of CH (yes/no), relatives with a CH diagnosis, time since first symptoms of CH, time since cCH diagnosis, any previous change over time for the CH phenotype, time since the beginning of the current period of attacks, duration of the last remission period (in weeks), usually have a remission period (yes/ no), length of remission period if applicable, ability to predict the start of attacks after a remission period (yes/no), seasonal beginning of cCH attack periods (yes/no), season where the cCH attack periods begin if applicable, usual duration of CH attack period (in weeks), usual start time of CH attacks (hourly intervals/unknown), usual number of CH attacks per day, usual duration of the attacks (in minutes), trigger factors (yes/no), which trigger factors if applicable, usual pain intensity, and the accompanying symptoms are also considered baseline disease characteristics. See Panel 3 for more details regarding the categories.

Panel 3 Categories for baseline disease characteristics

Variable	Categories
Treatment failures	Lack of efficacy, safety/tolerability, contraindication, participant in remission period, other
Relatives with a CH diagnosis	Mother, father, sister, brother, mother's mother, mother's father, father's mother, father's father, daughter, son
Change over time for CH phenotype	No, from episodic to chronic, from chronic to episodic back to chronic
Length of remission period	<1 month, 1 month <= and < 2 months, 2 months <= and <= 3 months
Season where cCH attack periods begin	Spring, summer, autumn, winter, other
Trigger factors	Alcohol, sleep, stress, other
Usual pain intensity	No pain or barely any pain, mild pain, moderate pain, severe pain, excruciating pain

The eDiary reported baseline efficacy variables that will be summarized are the number of weekly attacks, number of times abortive medication (triptans and/or oxygen, oxygen, triptans) was used weekly, weekly integrated measure of frequency and intensity of attack related pain, average attack related daily pain score, and average pain per attack, which are all collected during the 28-day Screening Period.

The other baseline efficacy variables that will be summarized are: SIS domain scores, EQ-5D-5L descriptive items as well as the visual analogue scale (VAS) scores of the overall health state, and WPAI:GH2.0 sub-scores.

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 SOC and preferred term.

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

Social history will be summarized.

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

10 Recent and Concomitant Medication

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

Medications will be classified according to the start and stop dates and summarized by anatomical therapeutic chemical (ATC) code level 4, and generic drug name. Handling of missing or incomplete dates is specified in section 23.4.3.

The following categories will be used:

- Prior: Medications with a start or stop date before first IMP infusion,
- Concomitant: Medications with a start date at or after the date of first IMP infusion, medications with a stop date at or after the date of first IMP infusion, medications with a start date before first IMP infusion and with no stop date (being ongoing at the end of the trial), and medications where both start and stop date are completely missing

The summaries will be repeated for CH medication (only prior), preventive medication, and transitional medication.

Transitional medications will be listed based on the APTS. The listing will include the generic drug name, indication, time since the first IMP, the duration, the start and end dates, and dosing information.

All disallowed medications will be listed based on the APTS. The listing will include the generic drug name, indication, time since the first IMP, the duration, the start and end dates, and dosing information.

The eDiary reported medications will be handled separately. For further details see section 13.5.8.

11 Exposure

The total number of infusions received, and total number of infusions completed as planned will be summarized.

Furthermore, for each infusion visit, the number of infusions received, completed as planned, temporarily interrupted, and lasted longer than 45(+15) minutes, as well as descriptive statistics for the duration of infusions and for the duration of the infusions that were temporarily or fully interrupted will be summarized.

Participants, who at any point during the trial received a different dose than what was planned, will be listed. The listing will include all infusion visits, dates of infusion visits, planned dose for the participant and actual dose received for the participant.

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

The number of participants with a 1-year exposure (for details see section 23.2.2) will be summarized.

The summaries will be based on the APTS.

12 eDiary Compliance

The number and proportion of participants with eDiary data will be summarized and presented by 1-week intervals. The summary will for each week include the number of participants in the trial for that week, the number and percentages of participants with data for that week, and for weeks with daily registrations the percentages of participants with 4, 5, 6 and 7 days of data.

A participant will count as being in the trial for a week if (s)he has at least 1 day with eDiary data in that week.

The summary will be based on the APES.

13 Efficacy

13.1 General Efficacy Analysis Methodology

All confidence intervals (CIs) will be two-sided 95% CIs.

13.2 Testing Strategy

No formal testing will be done.

13.3 Analysis Methodology for the Primary Endpoints

There are no primary efficacy endpoints. The primary endpoints are safety endpoints that will be described in chapter 14.

13.4 Analysis Methodology for the Key Secondary Endpoints

There are no key secondary efficacy endpoints.

13.5 Analysis Methodology for the Secondary and Exploratory Endpoints

13.5.1 Short-term Efficacy Estimand

The short-term efficacy estimand is the mean change from Baseline in the weekly number of attacks (Weeks 1-4) for participants with chronic cluster headache receiving IV infusion of eptinezumab 400 mg every 12 weeks, without the use of transitional treatment (GON block and oral steroids), and regardless of the use of abortive and preventive medication for cluster headache, and infusion interruption or termination before full dose is received.

Clinical Question of Interest

The clinical question of interest is changes in cluster headache symptoms within the first 4 weeks after infusion with eptinezumab 400 mg.

Attributes of the Short-term Efficacy Estimand

The short-term efficacy estimand has the following attributes:

- The **treatment condition of interest** will be IV infusion of eptinezumab 400 mg every 12 weeks, with or without the use of abortive and preventive medication for cluster headache
- The **population of interest** will be participants with cCH
- The **endpoint to be obtained to address the clinical question** is change from Baseline in the weekly number of attacks (Weeks 1-4)
- The **intercurrent event** use of transitional treatment will be addressed by a hypothetical strategy estimating the efficacy, in the hypothetical scenario where no transitional treatment is available, while interruption or termination of IMP such that full dose is not received will be addressed by a treatment policy strategy
- The **population level summary** will be the mean change across weeks 1-4

13.5.1.1 Rationale for the Short-term Efficacy Estimand

The number of weekly attacks is considered a good measure of the impact of IV infusion of eptinezumab 400 mg every 12 weeks, since it captures an important part of the symptoms for cluster headache and therefore change from Baseline in the average number of weekly attacks will be used as the endpoint for the efficacy estimand described in details in section 13.5.1.

Justification of Treatment Condition of Interest

The use of abortive medication (triptans and oxygen) 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 participants suffering from chronic cluster headache. Furthermore, though the use of preventive medication could influence the number of attacks, the potential effect is expected to be limited in a chronic cluster headache population. Thus, the use of preventive medication is not considered to be an intercurrent event.

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.

- Use of transitional treatment (GON block and oral steroids) – hypothetical strategy

  Use of transitional treatment could change the disease status considerably, and thus influence the number of attacks. In a study, 35% of the participants taking the oral steroid prednisone experienced a complete cessation of cluster headache attacks after 7 days compared to 7% in the placebo group and 49% taking prednisone experience at least a 50% reduction of cluster headache attacks compared to 15% for the placebo group after 7 days.[1] To get a clearer picture of the change in symptoms after infusion with eptinezumab, a hypothetical strategy has been chosen to address this, estimating the effect if no transitional treatment was available, using the 7 day limit[1] as described in section 23.2.1.5. Due to the expected positive effect of transitional treatment this is considered a conservative approach.

- Interruption or termination of IMP such that full dose is not received – treatment policy strategy

  If an IMP is stopped prematurely (either temporarily or completely) the consequence is that the participant did not receive all of the intended dose of eptinezumab and it could be expected that the potential effect of eptinezumab could be decreased due to the lower dose. To be conservative, a treatment policy strategy is used to address this.

13.5.1.1.1 Missing Data

Details of imputation of missing data are provided in section 23.2.1.3.

13.5.1.2 Estimator

To estimate the change from Baseline in the number of weekly attacks (Weeks 1-4) described above, a Mixed Model for Repeated Measurements (MMRM) using a restricted maximum likelihood (REML)-based approach will be used. The data used for the MMRM is FAS and DPS2. The MMRM will include the following fixed effects: week (1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40), and country (for details see section 23.2.3) as factors, logarithm of the baseline score as a continuous covariate, and the logarithm of the baseline score-by-week interaction. An unstructured covariance structure will be used to model the within-participant errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The change from Baseline in the number of weekly attacks (Weeks 1-4) will be estimated as the average from the least squares estimates from the MMRM for the week effect using the contrast [1, 1] [1, 2] [1, 3] [1, 4] /divisor = 4. The SAS® code for the analysis is shown in Appendix II. If this analysis fails to converge the following covariance structures will be tried out:

- UN(15) - banded unstructured
- UN(14) - banded unstructured
- UN(13) - banded unstructured
- UN(12) - banded unstructured
- TOEPH – heterogenous Toeplitz
- CSH – heterogenous compound symmetry
- TOEP - Toeplitz
- CS - Compound Symmetry

and the one with the lowest AIC amongst the ones that converged will be applied. In case of no models converging, the results will only be shown as described in chapter 7.

13.5.2 Additional Short-term Efficacy Estimand

In addition to the short-term efficacy estimand described in section 13.5.1 the population level summary ‘mean change across weeks 1-2’ will be considered with everything else as described in section 13.5.1 except that the contrast used is [1, 1] [1, 2] /divisor = 2.

13.5.3 Long-term Efficacy Estimand

The long-term efficacy estimand is the mean change from Baseline in the monthly number of attacks (Months 1-12) for participants with chronic cluster headache receiving IV infusion of eptinezumab 400 mg every 12 weeks, without the use of transitional treatment (GON block and oral steroids), and with continuation of treatment eptinezumab 400 mg for 12 months, and regardless of use of abortive and preventive medication for cluster headache, and infusion interruption or termination before full dose is received.

The approach described in section 13.5.1 also apply for the long-term estimand with a few adjustments:

- The **clinical question of interest** is changes in cluster headache attacks within the 12 months after infusion with eptinezumab 400 mg.
- The **endpoint to be obtained to address the clinical question** is change from Baseline in the monthly number of attacks (Months 1-12)
- The **population level summary** will be the mean change across Months 1-12
- The **intercurrent events** use of transitional treatment and interruption or termination of IMP such that full dose is not received will be handled as in section 13.5.1. Furthermore, when the primary reason is either "Lack of Efficacy" or "Adverse Events" for withdrawal from treatment this will be considered an intercurrent event that will be handled by a hypothetical strategy

Intercurrent Events

In addition to the intercurrent events described above, the following intercurrent event, occurring after treatment initiation and potentially affecting either the interpretation or the existence of the measurements associated with the clinical question of interest, is considered.

- Withdrawal from treatment due to "Lack of Efficacy" or "Adverse events" – Hypothetical strategy

For participants withdrawing from treatment, the majority of the effect is expected to be seen within the first 12 weeks following their last infusion and therefore data that occur beyond 12 weeks after their last infusion will not be considered.

Estimator

The intercurrent event withdrawal from treatment will be handled by a hypothetical strategy estimating the effect where all participants continue their treatment with eptinezumab 400 mg for 12 months by not including data collected 3 months or more after the latest infusion.

Furthermore, the following adjustments are needed compared to the estimator in section 13.5.1

- The week variable in the MMRM will be replaced by Month 1 to 12
- The DPS2 will be replaced by DPS3
- The contrast that will be used is given as [1, 1] [1, 2] [1, 3] [1, 4] [1, 5] [1, 6] [1, 7] [1, 8] [1, 9] [1, 10] [1, 11] [1, 12] /divisor = 12

13.5.4 Rationale for the Efficacy Endpoints following the strategy of the Long-term Efficacy Estimand

Regarding the efficacy endpoints based on the number of cluster headache attacks, intensity of pain or use of abortive medication, the data handling will follow the strategies described in section 13.5.3. For all of these endpoints, the intercurrent events use of transitional treatment

and interruption or termination of IMP such that full dose is not received and withdrawal from treatment will be handled as described in section 13.5.3.

For endpoints based on the number of attacks the rationale is the same as previously described. For endpoints based on intensity of pain the same strategies are used since not getting the full dose (by interruption/termination of IMP or withdrawal from treatment) is expected to also affect the pain as well as use of transitional treatment is expected to decrease the pain severity.[1] For endpoints based on the use of abortive medication, not getting the full dose (by interruption/termination of IMP or withdrawal from treatment) is expected to also affect the use of abortive medication. Furthermore, the use of transitional treatment is expected to reduce the number of attacks and therefore is also expected to reduce the number of times abortive medication can be used.

13.5.5 Intercurrent Events and Withdrawal from Treatment

The number of participants who experienced the intercurrent event "use of transitional treatment" and "interruption or termination of IMP such that full dose is not received" during Weeks 1-4 will be summarized for the short-term efficacy estimand defined in sections 13.5.1 and 13.5.2.

The number of participants who experienced the intercurrent events "use of transitional treatment", "interruption or termination of IMP such that full dose is not received" and "withdrawal from treatment" during Months 1-12 will be summarized for the long-term efficacy estimand following the definition in section 13.5.3.

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

Participants who withdrew from treatment will be listed and the listing will include the number of days in the trial until withdrawal from treatment, the number of days since the last IMP, and the primary reason for withdrawal, and all reasons for withdrawal.

13.5.6 Efficacy Analysis

13.5.6.1 Continuous Efficacy Endpoints

In the eDiary, information regarding number of attacks, level of severity of pain of the attack(s) as well as use of abortive medication is gathered daily or weekly. When analysing data from the eDiary, three different data structures will be considered: weekly scores based on daily data, monthly scores based on weekly scores (regardless of the weekly scores originating from data being daily or weekly), and weekly scores based on either daily or weekly reported data covering all weeks which will be used descriptively to show the data over time (for further details see section 23.1). The endpoints listed below are covered by applying the three different data structures in the MMRM as in section 13.5.1.2 using FAS and DPS3 with the relevant time variable, appropriate baseline value (for endpoints considering weekly/monthly attacks and integrated measure the log-transformed baseline

values will be used for all other endpoints there will be no transformation of the baseline values), and the appropriate contrast statement as well as a different list of covariance structures to get estimates of mean values, their standard errors (SEs) as well as two-sided 95% CIs:

- Change from Baseline in the weekly number of times an abortive therapy (oxygen and/or triptans) was used (Weeks 1-4, 13-16, 25-28, 37-40)
- Change from Baseline in the number of weekly attacks (Weeks 1-4, 13-16, 25-28, 37-40)
- Change from Baseline in the average attack related daily pain (including days with no attacks), as assessed using the 5-point self-rating pain severity scale (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40)
- Change from Baseline in the number of monthly attacks (Months 1,2, …, 12)
- Change from Baseline in the pain per attack assessed by the 5-point self-rating pain severity scale scores (Months 1,2, …, 12)
- Change from Baseline in the monthly number of times an abortive therapy (oxygen and/or triptans) was used (Months 1,2, …, 12)
- Change from Baseline in the weekly integrated measure of frequency and intensity of attack related pain, that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during a week (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) or the intensity of attack related pain multiplied by the weekly number of attacks (Weeks 5, 6, …, 12, 17, 18, …, 24, 29, 30, …, 36, 41, 42, …, 48)

Continuous endpoints using weekly scores based on daily data will first use an unstructured covariance structure. If this analysis fails to converge the following covariance structures will be tried out:

- UN(15) - banded unstructured
- UN(14) - banded unstructured
- UN(13) - banded unstructured
- UN(12) - banded unstructured
- TOEPH – heterogenous Toeplitz
- CSH – heterogenous compound symmetry
- TOEP - Toeplitz
- CS - Compound Symmetry

and the one with the lowest AIC amongst the ones that converged will be applied.

Continuous endpoints using monthly scores will first use an unstructured covariance structure. If this analysis fails to converge the following covariance structures will be tried out:

- UN(11) - banded unstructured
- UN(10) - banded unstructured
- UN(9) - banded unstructured
- TOEPH – heterogenous Toeplitz
- CSH – heterogenous compound symmetry
- TOEP - Toeplitz

- CS - Compound Symmetry

and the one with the lowest AIC amongst the ones that converged will be applied.

Weekly scores based on daily or weekly reported data will try out the following list of covariance structures:

- CSH – heterogenous compound symmetry
- TOEP - Toeplitz
- CS - Compound Symmetry

and the one with the lowest AIC amongst the ones that converged will be applied.

In addition to estimates, SEs and CIs the following estimates will be calculated:

- Change from Baseline in the number of weekly attacks, the weekly pain per attack score, the average attack related daily pain, the weekly integrated measure of frequency and intensity of attack related pain, and the weekly number of times an abortive therapy was used for Weeks 1-2 and Weeks 1-4 using data type 1)
- Change from Baseline in the number of monthly attacks, the monthly pain per attack score, the monthly integrated measure of frequency and intensity of attack related pain, and the monthly number of times an abortive therapy was used for Months 1-3, Months 4-6, Months 7-9, Months 10-12, Months 1-6, Months 7-12 and Months 1-12 using data type 2)

Each SIS domain score, the EQ-5D-5L VAS and each WPAI:GH2.0 sub-score will be analysed using the MMRM from section 13.5.1.2 considering FAS with the relevant time variable and appropriate baseline value (not log-transformed) as well as the same approach for choice of covariance structure to be applied.

PGIC will be analysed using the MMRM from section 13.5.1.2 considering FAS with the relevant time variable and no baseline value as well as the same approach for choice of covariance structure to be applied.

13.5.6.2 Efficacy Endpoints Regarding Response

For endpoints regarding response (30%, 50%, 75% or 100%) or sustained response (75%), the number and percentage of responders using weekly number of attacks for Week 1, Week 2, Week 3, Week 4, Week 5, …., Week 48 and the number and percentage of responders using monthly number of attacks for Month 1, Month 2, …, Month 12 will be presented without imputations other than described in section 13.5.1.1.1. Additionally, sensitivity analyses will be made using LOCF and worst case imputations, for further details see section 13.5.9.3. For all of these analyses DPS3 will be used when determining whether a participant is a responder or not.

Furthermore, the number and percentage of responders will be found for the following periods of time (for details see section 23.2.1.7):

- Months 1–3, Months 4-6, Months 7-9, Months 10-12
- Months 1-6, Months 7-12

- Months 1-12

13.5.6.3 Other Efficacy Endpoints

Endpoints that are not covered by sections 13.5.6.1 and 13.5.6.2 will only be summarized descriptively as described in chapter 7.

13.5.6.4 Subgroup Analyses

The subgroups to be investigated are participants who are treatment resistant and participants who are not (see section 23.2.5 for a definition of treatment resistant). The endpoint to be considered for these subgroup analyses is Change from Baseline in the number of monthly attacks (Months 1,2, …, 12).

13.5.7 Rationale for Selected Analysis Method for the Secondary and Exploratory Endpoints

The MMRM model is chosen as it is a very flexible and robust analysis, and with the selected explanatory variables it will allow the endpoint to vary freely by visit, account for the baseline level and for country differences, and it includes the most flexible structure for within participant variation. This will allow the use of all participants also those who withdraw or have missing data.

13.5.8 eDiary Reported Use of Medication

In the headache eDiary, participants are asked each day or each week (depending on whether a participant is in a period with daily or weekly registrations) to fill out whether they used any of the following medications during that day/week: oxygen, triptans, or other. The number and percentage of participants taking each of the medication types will be presented for each 4-week interval in the trial including baseline values.

13.5.9 Sensitivity Analyses of Secondary and Exploratory Endpoints

13.5.9.1 Sensitivity Analyses to assess the impact of the use of transitional medication

To assess the impact of the use of transitional treatments, the MMRMs described in sections 13.5.1 and 13.5.3 will be used to analyse data where all data are included also immediately after receiving a transitional treatment corresponding to a treatment strategy. It will only be done for the endpoints described in sections 13.5.1 and 13.5.3 respectively.

13.5.9.2 Sensitivity Analyses to assess the impact of the strategy of handling withdrawal from treatment

To assess the impact of the chosen hypothetical strategy for handling withdrawal from treatment the MMRM described in section 13.5.3 will be used to analyse data where all data

are included corresponding to a treatment strategy. It will only be done for the endpoint described in section 13.5.3.

13.5.9.3 Sensitivity Analyses to assess the impact of missing data regarding response

To assess the impact of only imputing data by prorating for response endpoints as described in section 13.5.6.2, LOCF and worst case imputations will be carried out for the endpoints regarding 75% response.

14 Safety

14.1 Adverse Events

14.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

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 participants with these adverse events.

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

Listings of adverse events will be sorted by site, treatment group, participant screening number, and adverse event start date, and include preferred term, investigator term, adverse event start date, the date of first IMP infusion, the date and time of the latest IMP infusion prior to the adverse event, the time since latest IMP infusion, duration of the adverse event, action taken, causality, intensity, seriousness, and outcome. Furthermore, sex, age, race and baseline weight will be presented if available. For adverse events that change in intensity, each intensity will be included. In listings of adverse events, start or stop dates will be displayed as collected also in case of partially or completely missing dates.

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 participant signed the *Informed Consent Form(s)* and prior to the date and time of first dose of eptinezumab

- *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 severity or becomes serious during or after administration of the first dose of IMP

For handling of adverse events with incomplete start dates to facilitate this classification, see section 23.4.4. Note that adverse events with incomplete start dates will be classified as not being treatment-emergent if the causality to IMP is "Not Related - Prior to IMP".

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

14.1.4 Presentation of Adverse Events

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

The numbers, and percentages of participants with TEAEs, TEAEs leading to infusion interruption, serious adverse events (SAEs), or adverse events leading to withdrawal, and of participants who died will be presented based on the APTS.

14.1.5 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided:

- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs by sex and preferred term
- TEAEs with an incidence ≥2% 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 the days of the first, second, third and fourth infusion)
- TEAEs by infusion Periods by SOC and preferred term (this includes time between the start of the first and second infusions, second and third infusions, third and fourth infusions, and within 12 weeks after the start of the fourth infusion)

14.1.6 Presentation of Deaths

All the adverse events in participants who died will be listed for the APES.

14.1.7 Presentation of Serious Adverse Events

All the SAEs will be listed for the APES.

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

14.1.8 Presentation of Adverse Events Leading to Withdrawal

All the AEs leading to withdrawal will be listed for the APES.

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

14.1.9 Presentation of Adverse Events leading to Trial Drug Infusion Interruption or Termination

All AEs leading to trial drug infusion interruption or termination will be listed for the APES.

TEAEs leading to trial drug infusion interruption or termination will be summarized based on APTS by:
- SOC and preferred term

14.1.10 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:
- AESIs by SOC and preferred term
- AESIs by SOC and preferred term, separately for each individual event category

The summaries will be provided for the APTS.

14.2 General Methodology for Other Safety Data

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

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

Descriptive statistics for the safety variables, both absolute values and changes from Baseline, will be presented by visit.

The number and percentage of participants with at least one PCS value at any post-baseline assessment time point will be summarized by variable. All available assessments will be included in the evaluation of PCS values.

For participants with post-baseline PCS values, listings will be provided including all the values for those participants for the variable, with flagging of PCS values and out-of-reference-range values.

All the adverse events in participants with post-baseline PCS values will be listed by participant screening number; the listing will include the PCS value, the assessment date, the change from Baseline in PCS value, the preferred term for the adverse event, and start date and stop date of the adverse event. The PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

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 2.

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

Fasting lipid and fasting glucose concentrations will be presented in separate tables from the overall laboratory tables.

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

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

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 >2×ULN
- alkaline phosphatase >1.5×ULN
- ALT or AST >3×ULN AND total bilirubin >1.5× or >2×ULN

Participants fulfilling any of the criteria will be listed, and the listing will include all the ALT, AST, bilirubin, and alkaline phosphatase values for those participants, 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 participants 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 participants who met any of the criteria specified above at any post-baseline visit will be summarized. In the summaries, each participant 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.

Descriptive statistics for the vital signs, weight, and BMI, both absolute values and changes from Baseline, will be presented by visit. The number of participants exceeding the PCS values will be tabulated.

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 in QTcF will also be summarized categorically by visit. 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 participants 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.

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 that collects a lifetime recall
- for the past 1 month at screening (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening 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, for example, from screening to Baseline
- post-baseline (using the *Since Last Visit Version*) – the C-SSRS assessments after Baseline

The numbers and percentages of participants with lifetime, past 1 month, baseline, or post-baseline suicide-related events based on the C-SSRS will be summarized. For each summary, the most severe item with an answer "Yes" for each participant according to the ordering given in Panel 4 is displayed. For the post-baseline assessments, the most severe score (Panel 4) per participants related to suicidal ideation and/or behaviour will be summarized.

The number and percentage of participants with *no suicidal ideation or behaviour* will be summarized.

Panel 4 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)	

The C-SSRS scores will be summarized based on the APTS for participants with at least one post-baseline C-SSRS assessment, regardless of whether they had a baseline C-SSRS assessment.

Missing C-SSRS scores will not be imputed.

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

For participants 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 participants.

15 Immunogenicity

For participants with pre-existing antibodies at Baseline, the number and percent of participants who are positive for anti-eptinezumab antibody will be summarized. In addition, for each scheduled visit and for the entire trial the number and percent of participants who are positive for anti-eptinezumab will be summarized. Denominators for percentages will be the number of participants with a sample taken for the specified visit. For participants with ADA, neutralizing properties of anti-eptinezumab antibodies will also be summarized. Participants with at least one visit with a positive ADA result (the confirmatory test being positive) will be considered as an ADA positive participant. Participants with no positive ADA results will be considered as ADA negative participants.

Participants' titer per visit and peak positive titer showing median, min, max and IQR for the peak values will be summarized.

Participants with first positive ADA result at the different visits and how many out of these had all the following results also being positive will be summarized. If missing values occur after a positive result this will also count as a following result being positive.

Participants with a positive anti-eptinezumab antibody result will be listed. The listing will include visit, sampling assessment date, final ADA result, titre result and final Nab result.

In addition, summaries of TEAEs by SOC and preferred term will be provided for participants who are ADA-positive as well as ADA-negative. Furthermore, summaries of TEAEs of Hypersensitivity and Anaphylactic Reactions by SOC and preferred term will be provided for participants who are ADA-positive as well as ADA-negative.

Furthermore, adverse events in participants with positive anti-eptinezumab antibody results or with pre-existing antibodies at Baseline will be provided. The listing will include the preferred term for the adverse event and start date and stop date of the adverse event.

16 Biomarker

The results from the analyses described in this section will be presented in an addendum to the clinical trial report.

The biomarker that will be presented is CGRP covered by the exploratory endpoint "Change from Baseline in CGRP (CGRP-eptinezumab complex, free CGRP) (Week 0 after IMP infusion, and Weeks 12, 24, 36, and 48)" and will be considered for the values measured prior to an IMP infusion as well as the values after an IMP infusion.

The baseline values of CGRP-eptinezumab complex and free CGRP will be summarized.

Numbers, arithmetic mean, standard deviation, median, lower and upper quartiles, minimum and maximum values as well as the percentage change from Baseline will be summarized by Visits before and after an IMP infusion for Weeks 12, 24 and 36 and once for Week 48.

The baseline value will be the value measured before the beginning of the first IMP infusion at the Baseline Visit.

For all other visits the acceptable ranges for measurements are defined as a value measured on the same date as an IMP infusion but prior to the IMP infusion being started is the measurement to be used as the prior value. A measurement made 55 minutes after the IMP infusion ended and the rest of that day will be assigned as the after IMP value.

17 Pharmacokinetic/Pharmacodynamic Analyses

A PK/PD analysis will be planned and conducted by PKPD modelling & simulation, H. Lundbeck A/S, and reported separately.

18 Data Reviews

The quality of the trial will be overseen by performing data reviews during the conduct of the trial. The reviews may include, but are not limited to, data quality, protocol adherence, and the appropriateness of design assumptions, including the sample size assumptions.

19 Interim Analyses

No interim analysis is planned.

20 Sample Size Considerations

In line with the ICH E1 guideline,[3] the trial aims at providing data in 100 participants exposed to eptinezumab for 1 year. Dodick (2020),[4] participants suffering from cCH included in a 12-week study, reports less than 4% withdrawals. In the European Union Drug Regulating Authorities Clinical Trials (EudraCT) report for study NCT02964338,[5] in participants suffering from cCH, approximately 7% of participants dropped out from the first 12-week period; the withdrawals due to the “sponsor terminated study” are not included as a reason for withdrawal. As the withdrawal rate for a long-term study like the current trial is unknown, 125 participants are planned to be enrolled and treated, allowing for 100 participants to complete, with a withdrawal rate of 20%. The withdrawal rate will be monitored during the trial conduct, and if a clear deviation from the assumed withdrawal rate is observed, the number of participants enrolled and treated might be increased to ensure that data is available for a sufficient number of participants with long-term exposure.

21 Statistical Software

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

22 Changes to Analyses Specified in the Protocol

In the definition of FAS monthly has been changed to weekly to accommodate that there are endpoints considering weekly data.

There has been a clarification of the phrasing of the endpoints from the protocol. Furthermore, the names of the different types of endpoints have also been changed to describe these in a concise way.

The following endpoints have been added for completeness:

- Response: ≥75% reduction from Baseline in the number of weekly attacks (Weeks 1-4, 13-16, 25-28, 37-40)
- Change from Baseline in the weekly integrated measure of frequency and intensity of pain, that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during a week (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39, 40) or the intensity of pain multiplied by the weekly number of attacks (Weeks 5, 6, …, 12, 17, 18, …, 24, 29, 30, …, 36, 41, 42, …, 48)
- Use of triptans (Weeks 1-48)
- Use of oxygen (Weeks 1-48)
- Use of preventive medication (Weeks 1-48)
- Response: ≥75% reduction from Baseline in the number of monthly attacks (Months 1,2, …, 12)
- Sustained response: ≥75% reduction from Baseline in the number of monthly attacks for any month, where all the subsequent Months also had ≥75% reduction from Baseline in the number of monthly attacks (Month 1,2, …, 12)
- A maximum score of mild in the 5-point self-rating pain severity scale (Months 1, 2, …, 12)
- Change from Baseline in the number of weekly attacks (Weeks 1-4 and Weeks 1-2)
- Change from Baseline in the number of monthly attacks (Months 1-12)

The estimand part of the efficacy analyses were not included in the protocol. It has been added to the SAP for clarification.

The baseline score is log-transformed for MMRMs using number of weekly attacks, number of monthly attacks and weekly integrated measure of frequency and intensity of attack related pain.

23 Details on Data Handling

23.1 Data Structure

Information used for the efficacy analyses is either coming from the eDiary or from visits (both site visits and phone contacts). The structure of data depends on the source (eDiary or visit) and will be handled differently.

Because of the structure in the eDiary, all information is collected at a daily basis or at a weekly basis. This gives the possibility to look at data in three different ways:

1. Using the first 4 weeks after each IMP infusion providing 16 weekly scores (Weeks 1, 2, 3, 4, 13, 14, 15, 16, 25, 26, 27, 28, 37, 38, 39 and 40)
2. Using the 12 monthly scores for the entire trial (Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12)
3. Using the 48 weekly scores for the entire trial (Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, …., 45, 46, 47 and 48)

The rationale for considering these different ways of using data is:

1. The first four weeks after each IMP infusion are the periods with the most precise information (the participants complete the eDiary on a daily basis) and more likely it will be possible to use the most appropriate covariance structure
2. The months use as much information as possible since monthly scores are imputed across 4 weeks
3. All weeks show in more detail the development across time during the entire trial with a limitation in the choice of variance structure

Thus, if numbers (estimates) can be found from MMRMs using more than one of the above data structures the order of preference is if the data structure in 1) is applicable for finding the number of interest use this, if 1) is not appropriate and 2) is appropriate use 2), if neither 1) or 2) is appropriate then use 3). More specifically, for endpoints considering Weeks 1-4, 13-16, 25-28, 37-40 the results from 1) will be the most valid, for endpoints considering Months 1,2, …, 12 the results from 2) will be the most valid, and for endpoints considering Weeks 1, 2, …, 48 the results from 3) will be the most valid. The endpoints considering intervals across Weeks 1 to 48:

- Conversion from cCH to episodic cluster headache (eCH): no cluster headache attacks for ≥3 consecutive months (≥12 consecutive weeks) (Weeks 1-48)
- cCH remission: no cluster headache attacks for ≥1 month (≥4 consecutive weeks) (Weeks 1-48)
- cCH remission: no cluster headache attacks for ≥1 month (≥4 consecutive weeks) (Weeks 1-12, 13-24, 25-36, 37-48)
- Use of transitional treatment (Weeks 1-48)
- Use of triptans (Weeks 1-48)
- Use of oxygen (Weeks 1-48)
- Use of preventive medication (Weeks 1-48)

do not fit into either of the data structures in 1), 2) or 3) but will be assessed by a yes if the participant is fulfilling the criteria in the endpoint.

The ePRO data measured in connection with visits will be looked at in one way: the relevant week numbers corresponding to the visits will be considered in the analyses.

23.2 Derived Variables

23.2.1 eDiary

23.2.1.1 The 5-point Self-rated Pain Severity Scale Scores

The 5-point self-rated pain severity scale scores are used for several endpoints expressing the intensity of pain in different ways using distinct formulas. Common for them all is, that if the number of cluster headache attacks is reported to be 0, the corresponding pain will be set to be the category expressing no pain (no pain/barely any pain) since a participant will not be asked to rate the pain when 0 attacks are reported. The scores used in the analyses will be 0 (no pain/barely any pain) to 4 (excruciating pain).

23.2.1.2 Calculation of Baseline eDiary Assessments

Calculation of the eDiary baseline begins on the day of the Screening Visit.

In case of a 7-day extension of the Screening Period the last 21 days of the original 28 days Screening Period and the first 7 days of the extension will be used to calculate the baseline value. In case the extension is less than 7 days more days will be used from the Screening Period ending up with a total of 28 days.

When finding the baseline value for number of monthly attacks, the number of reported attacks will be scaled up to 28 days using (assuming that days with missing data are similar to the days with data):

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

The average weekly number of attacks at baseline will be found by dividing the number of monthly attacks at baseline by 4:

28(Reported number of attacks/Reported eDiary Days)/4*

When finding the baseline number of times abortive medication was used the above formulas are used with *Reported number of attacks* replaced by *Reported number of times an abortive medication was taken*.

When finding the baseline values using the 5-point self-rated pain severity scale scores, three different formulas will be used. The **baseline monthly pain per attack** is found by:

Sum of reported pain across attacks/Number of reported attacks

The **baseline weekly pain per attack** equals the baseline monthly pain per attack.

The **baseline average attack related daily pain** is found by:

Sum of the average daily pain across days with data/Number of days with data

where days with 0 attacks will add a value of 0 to the nominator and count as a day in the denominator.

The **baseline monthly integrated measure of frequency and intensity of attack related pain** is found by:

*((Sum of reported pain across days with data/Number of days with data)*28)/4*

where days with 0 attacks will add a value of 0 to the nominator and count as a day in the denominator.

The **baseline weekly integrated measure of frequency and intensity of attack related pain** equals the baseline monthly integrated measure of pain.

23.2.1.3 Imputation of Missing Post-baseline eDiary Assessments

The strategy of imputation of missing values is given by:

1. For each weekly score in the periods with daily entries in the eDiary, prorating is used to impute any missing data when data have been observed for at least 4 days in a week, to have full weekly scores
2. For each monthly score, prorating is used to impute any missing data when data have been observed for at least 2 weeks in a month (after prorating weekly scores), to have full monthly scores

For a 7-day weekly period where the eDiary is completed in at least 4 out of 7 days, the number of attacks will be calculated using prorating:

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

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

For a 4-week monthly period where the eDiary is completed in at least 2 out of 4 weeks, the number of attacks will be calculated using prorating:

4(Number of weekly attacks/Reported eDiary Weeks)*

For participants where the eDiary is completed in 1 week or less the 4-week monthly observation will be set to missing.

Use of abortive medication is prorated using the same criteria and formulas as above where *Reported number of daily attacks* is replaced by *Reported number of daily times an abortive medication was taken* and *Number of weekly attacks* is replaced by *Number of weekly times an abortive medication was taken*.

The severity of attacks is prorated using the same criteria as above using the same formulas as in section 23.2.1.2.

The derivation of the three pain scores can be seen in Panel 5. When calculating the average attack related daily pain and the weekly integrated measure of frequency and intensity of attack related pain, a value of 0 will be added to the nominator and count as a day in the denominator for days/weeks with 0 attacks. Furthermore, the weekly pain per attack is not defined for days/weeks with 0 attacks.

Panel 5 Definitions of Post-Baseline Pain Scores

	Daily eDiary	Weekly eDiary
Average attack related daily pain	Sum of the average daily pain across days with data/number of days with data	NA
Weekly pain per attack	Sum of pain across attacks/number of attacks	Pain
Monthly pain per attack	Sum of the weekly pain per attack scores/ number of the weekly pain per attack scores	
Weekly integrated measure of frequency and intensity of attack related pain	(Sum of pain across days with data /days with data)*7	Pain*number of attacks
Monthly integrated measure of frequency and intensity of attack related pain	Sum of the weekly integrated measure of frequency and intensity of attack related pain scores/ number of the weekly integrated measure of frequency and intensity of attack related pain scores	

23.2.1.4 Assigning Week to eDiary Assessments

The day of an infusion starts a new week e.g. the day of the first infusion is the first day of Week 1.

Weekly assessments coming from the eDiary will be assigned to a week using the day of an infusion as a starting point. Thus, the windowing showed in Panel 6 will be applied.

Panel 6 Windowing of Weeks – Weekly eDiary Assessments

Days since IMP	First IMP	Second IMP	Third IMP	Fourth IMP
28 to 37	Week 5	Week 17	Week 29	Week 41
38 to 44	Week 6	Week 18	Week 30	Week 42

Days since IMP	First IMP	Second IMP	Third IMP	Fourth IMP
45 to 51	Week 7	Week 19	Week 31	Week 43
52 to 58	Week 8	Week 20	Week 32	Week 44
59 to 65	Week 9	Week 21	Week 33	Week 45
66 to 72	Week 10	Week 22	Week 34	Week 46
73 to 79	Week 11	Week 23	Week 35	Week 47
80 until the next IMP	Week 12	Week 24	Week 36	Week 48

23.2.1.5 Calculation of Assessments for Intercurrent Events

Withdrawal from Treatment

When considering withdrawal from treatment data that are collected 3 months or more after the latest infusion will be excluded. Thus, for the daily entries, data occurring 84 days or more after the date for withdrawal from treatment will be removed. For the weekly entries, if at least one day of the 7-day period is covered by 84 days or more then data will be removed.

Use of Transitional Treatment

When considering the use of transitional treatment, data are excluded 7 days after the use of transitional treatment. Thus, for the daily entries, data that occur on 1 to 7 days after the date of use of transitional treatment will be removed. For the weekly entries, if the 7-day period is including at least 1 of the days in the 7-day period after use of transitional treatment data will be removed.

23.2.1.6 Calculation of Assessments for Sensitivity Analyses

When doing the sensitivity analyses of the use of transitional treatment and withdrawal from treatment data will contain all data when considering the prorating.

23.2.1.7 Response

For the periods of time a participant will be eligible to count as a responder if at least 50% of the weeks are observed and:

- For 3-months intervals: at least 2 out of 3 months are observed
- For 6-months intervals: at least 4 out of 6 months are observed
- For 12-months intervals: at least 8 out of 12 months are observed

For participants fulfilling these criteria the average reduction of number of monthly attacks will be calculated and compared to the response threshold to evaluate if the participant is a responder. When finding the percentage of responders, the denominator will be the number of participants who fulfil these criteria.

23.2.1.8 Conversion from cCH to eCH

Conversion is measured as ≥12 consecutive weeks with 0 attacks. For a participant to experience a conversion from cCH to eCH the following criteria must be fulfilled:

- The series of weeks should start with a week with 0 attacks
- The series of weeks should end with a week with 0 attacks
- At least 50% of the of the weeks should be observed (corresponding to 7 weeks)
- The series should consist of at least 13 consecutive weeks with 0 attacks or missing data fulfilling the above criteria.

23.2.1.9 Remission

For a participant to be in remission for the period listed in the endpoint the following should be fulfilled:

- The series of weeks should start with a week with 0 attacks
- The series of weeks should end with a week with 0 attacks
- All observed weeks should have 0 attacks
- A maximum of 1 missing week
- The series should consist of at least 4 consecutive weeks (which should all be in the period listed in the endpoint)

23.2.2 1-year Exposure

For a participant to count as a having a 1-year exposure the following should be fulfilled:

- A participant should have had 4 infusions with eptinezumab
- A participant should have been followed for at least 365 days after their first infusion. Thus, there should be some data/contact/visit with a date that is 365 days or more after first infusion with eptinezumab

23.2.3 Country

Countries with at least 20 participants will be kept individually, and countries with less than 20 participants will be combined into one country called “other”.

23.2.4 Use of Transitional Treatment

To address the endpoint Use of transitional treatment (Weeks 1-48), use of a transitional treatment will be collected from the “Transitional and Preventive Treatment for Cluster Headache Log” and in case of no findings, a participant will get a corresponding value of 0 for number of times a transitional therapy was used.

If a participant withdraws, any transitional treatment that is collected from the form will be considered up until 48 weeks after the first IMP infusion.

23.2.5 Treatment Failure

A treatment failure is defined as stopping a preventive medication with the reason being lack of efficacy, safety/tolerability or contraindications.

23.2.6 Treatment Resistant

The definition of a participant being treatment resistant is inspired by a published guideline[6] and the following criteria should be fulfilled for a participant to be treatment resistant:

1. At least 12 severe CH attacks during the Screening Period
2. At least three treatment failures with three different preventive medications prior to the Screening Visit

23.2.7 Sustained Response

A participant will be eligible to count as a sustained responder if:

- The first month is a response
- At least 50 % of the following months are observed
- Month 12 should be observed
- All observed months from the first month until Month 12 is a response

23.2.8 Maximum Score of Severity of Pain

The maximum score of severity of pain should be mild. In case of weeks with 0 attacks the severity will be considered to be mild or less. Furthermore, data need to have been observed for at least 4 days in a week to be able to assess if a participant fulfils the criterion about maximum score of severity being mild.

23.2.9 Patient Global Impression of Change (PGIC)

The PGIC is a single participant-reported item reflecting the participant's impression of change in their disease status since the Baseline Visit (that is, in relation to activity limitations, symptoms, emotions, and overall quality of life). The item is rated on a 7-point scale, where a low score indicate improvement from 1 (very much improved) to 7 (very much worse).

23.2.10 Sleep Impact Scale (SIS)

The SIS[7] is a participant-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 on: 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). Items within each domain were summed and transformed using the formula [(sum of the items – number of the items)/ range of the domain] * 100 yielding a score on a 0-100 scale.

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

Due to the technical build it will not be possible to have some missing values for a visit. Either all values will be there or none.

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

The EQ-5D-5L[8] is a participant-reported assessment designed to measure the participant's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS 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.

Due to the technical build it will not be possible to have some missing values for a visit. Either all values will be there or none.

23.2.12 Health Care Resource Utilization (HCRU)

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

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

The WPAI:GH2.0[9] is a participant 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 assess employment (yes/no); 3 items assess the number of hours worked, the number of hours missed from work due to the participant's condition, or due to other reasons; and 2 visual numerical scales to assess how much the participant's condition affects their productivity at work and their ability to complete normal daily activities.

The derivation of the WPAI:GH2.0 sub-scores[10] is given in Panel 7, where Q1-Q6 refers to question 1-6 in the questionnaire.

Panel 7 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 loss score will be set to missing.

23.2.14 Withdrawal from Treatment

When a participant withdraws from study it is not necessary to also fill out a "withdrawal from treatment" form. Thus, some participants will only have entered information about withdrawal from study. However, when a participant withdraws from study prior to receiving the fourth infusion with eptinezumab, a withdrawal from study is also relevant to be regarded as a withdrawal from treatment. Therefore, when a participant withdraws from study prior to receiving the fourth infusion and if there is no withdrawal from treatment for that participant the withdrawal from study will be used to define withdrawal from treatment. The time of withdrawal from treatment will be the same as the time of withdrawal from study. If the primary reason for withdrawal from study is either "lack of efficacy" or "adverse events" then the primary reason for withdrawal from treatment will be the same as the primary reason for withdrawal from study. All other primary reasons for withdrawal from study will be defined as "other" for the primary reason for withdrawal from treatment. All other reasons for withdrawal will not be inherited from withdrawal from study to withdrawal from treatment. When the "Withdrawal from treatment" form was filled out all reasons for withdrawal from treatment will be used.

23.3 Assigning Data to Visits

See section 3.1 for definition of baseline values.

23.3.1 Clinical Outcome Assessments (COAs) - Scales

For a participant withdrawing prior to the Completion Visit, the Withdrawal Visit will also include efficacy evaluations (PGIC, SIS, EQ-5D-5L, HCRU, and WPAI:GH2.0). Assessments from PGIC will be assigned to a Visit based on the windowing in Panel 8. Assessments from SIS will be assigned to a Visit based on the windowing in Panel 9. Assessments from EQ-5D-5L, HCRU, and WPAI:GH2.0 will be assigned to a Visit based on the windowing in Panel 10. In case of duplicate scale assessments in relation to a nominal visit the assessments from the Withdrawal Visit will be used.

Panel 8 Visit Windows – PGIC

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 3	4	28	1-42
Visit 4	8	56	43-70
Visit 5	12	84	71-98
Visit 6	16	112	99-126
Visit 7	20	140	127-154
Visit 8	24	168	155-182
Visit 9	28	196	183-210
Visit 10	32	224	211-238
Visit 11	36	252	239-266
Visit 12	40	280	267-294
Visit 13	44	308	295-322
Visit 14	48	336	> 322

Panel 9 Visit Windows – SIS

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 3	4	28	1-56
Visit 5	12	84	57-98
Visit 6	16	112	99-140
Visit 8	24	168	141-182
Visit 9	28	196	183-224
Visit 11	36	252	225-266
Visit 12	40	280	267-308
Visit 14	48	336	>308

Panel 10 Visit Windows – EQ-5D-5L, HCRU, and WPAI:GH2.0

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 3	4	28	<84
Visit 6	16	112	84 <= and <168
Visit 9	28	196	168 <= and < 252

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 12	40	280	252 <= and < 308
Visit 14	48	336	308 <=

Unscheduled visits will not contain assessments of the COAs mentioned above. In relation to the nominal visits post-baseline, a participant can complete their COAs 3 days before the visit. In case of duplicate scale assessments in relation to a nominal visit, i.e. if a participant fills out the scales 3 days before the visit and the visit is postponed afterwards implying that the participant has to complete the COA again, the latest assessment will be used.

Assessments done at Visit 2 for EQ-5D-5L, SIS, HCRU, and WPAI:GH2.0 will be assigned as the baseline value regardless of timing in relation to the IMP infusion.

23.3.2 Safety Variables

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

Laboratory Tests and ECG

Assessments of laboratory tests and ECGs at unscheduled visits and withdrawal visits will be assigned to a nominal visit according to the visit windowing specified in Panel 11 for participants in the APTS. Assessments for participants not receiving any infusions of IMP will be assigned to the Baseline Visit.

Panel 11 Visit Windows – Laboratory tests, ECG

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 1 (Screening Visit)	-4	-28	Before day 0 and before first IMP infusion
Visit 2 (Baseline Visit)	0	0	Same day as first IMP infusion (Day 0) and prior to IMP infusion on that date
Visit 5	12	84	After start of first IMP infusion to start of Visit 5 IMP infusion
Visit 8	24	168	After start of Visit 5 IMP infusion to start of Visit 8 IMP infusion

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 11	36	252	After start of Visit 8 IMP infusion to start of Visit 11 IMP infusion
Visit 14	48	336	After start of Visit 11 IMP infusion

Vital Signs

Vital signs will be assessed before and after infusion at nominal visits. For unscheduled or withdrawal visit assessments of vital signs, the values will be assigned a nominal visit according to Panel 12, and for scheduled visits where no IMP was given the assessment will be windowed to the pre-dose assessment at the nominal visit.

Panel 12 Visit Windows – Vital Signs (Pulse rate, Blood Pressure, Temperature)

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Visit 1 (Screening Visit)	-4	-28	Before day 0 and before first IMP infusion
Visit 2 (Baseline Visit) pre-dose	0	0	Same day as first IMP infusion (Day 0) and prior to IMP infusion on that date
Visit 2 (Baseline Visit) post-dose	0	0	After start of first IMP infusion to day 42
Visit 5 pre-dose	12	84	Day 43 to start of Visit 5 IMP infusion
Visit 5 post-dose	12	84	After start of Visit 5 IMP infusion to day 126
Visit 8 pre-dose	24	168	Day 127 to start of Visit 8 IMP infusion
Visit 8 post-dose	24	168	After start of Visit 8 IMP infusion to day 210
Visit 11 pre-dose	36	252	Day 211 to start of Visit 11 IMP infusion
Visit 11 post-dose	36	252	After start of Visit 11 IMP infusion to day 294
Visit 14	48	336	> 294

Height and Weight

Height is only assessed at the screening visit and weight is assessed once at each nominal visit. Windowing of these parameters will follow the windowing used for Laboratory tests and ECG.

23.4 Handling Missing or Incomplete Dates/Times

23.4.1 Withdrawal Date

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

23.4.2 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.

23.4.3 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 23.4.4. Furthermore when the start date is completely missing for medications collected at the Screening Visit, the medication start date is imputed with the date of the Screening Visit.

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
- If the stop date collected at the Screening Visit is completely missing and the medication is not being recorded as an ongoing medication, then the medication stop date is imputed with the date of the Screening Visit.

23.4.4 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 or for ongoing adverse events.

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

Start Dates

Participants with no IMP infusion

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

- UK-MMM-YYYY: The start date will be imputed with either the 1st of the month, or date of the Baseline Visit. Date of the Baseline Visit 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 the Baseline Visit. Date of the Baseline Visit 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 the Baseline Visit.

Participants who received at least one IMP infusion

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

- UK-MMM-YYYY:
  - If the year and month are equal to the year and month of treatment start date, the adverse event start date is imputed with the date of 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
- DD-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 DD-DEC-YYYY
  - If the year is after the year of treatment start date, the adverse event start date is imputed with DD-JAN-YYYY

- If the AE start date is completely missing:
  - If the AE stop date is not missing and is before the treatment start date, the adverse event start date is imputed with the AE stop date
  - If the AE stop date is not missing and is after the treatment start date, the adverse event start date is imputed with the treatment start date
  - If the AE stop date is missing (either completely or partially), the adverse event start date is imputed with the 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.

23.5 Data with Multiple Records

23.5.1 Dose Changes in Medication

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 Treatment-emergent AEs and Changes in Intensity or Seriousness of Adverse Events

An AE spans an interval in time, and in data it is potentially divided into several sub-intervals to ensure that within each sub-interval the status is the same for the whole interval. This could lead to multiple records for an AE as described in Panel 13.

Panel 13 Definition of Multiple Records

Event	Details	TEAE flag
AE starts at or after first dose of IMP	AE event created (start and possibly stop dates and AE characteristics are described)	• TRTEMFL=”Y”
Change in intensity	AE is split in 2 rows: Before and after change, so each part has the correct intensity	• If prior to first IMP => TRTEMFL = “ ” • If at or after first IMP AND intensity increase => TRTEMFL=”Y” • If at or after first IMP AND intensity decrease => TRTEMFL =” “
AE becomes SAE	If an existing AE becomes an SAE the AE is split in 2 rows: Before and after the datetime of the SAE occurrence. The AE is marked as SAE from this point and onwards.	• If prior to first IMP => TRTEMFL = “ “ • If at or after first IMP => TRTEMFL=”Y”
Events that do not happen simultaneously and with same precision on datetime, handle individually as above. Unknown time will be considered later than known time points. For events where multiple changes occur that do not happen simultaneously, extra rows are added for each change; for instance, will an AE with an intensity change and a change in seriousness be split into 3 rows: 1 for the original AE when it starts, 1 for the intensity change and 1 for the serious change.		
Events that happen simultaneously: SAE and change in intensity	An existing AE will be split in 2 rows: Before and after the event	• If prior to first IMP => TRTEMFL = “ ” • If at or after first IMP => TRTEMFL=”Y” (due to SAE, regardless of the direction of the intensity change)

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Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Trial title: Interventional, open-label, fixed-dose multiple administration study to evaluate long-term treatment with eptinezumab in participants with chronic cluster headache

Trial No.: 19385A

SAP date: 29 June 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

Short-term Efficacy Estimand

The SAS® code for the analysis of the short-term efficacy estimand described in Section 13.5.1 is given below. Here it is assumed that the ordering of the week factor is week 1, week 2, week 3, week 4, …

```
proc mixed data=DPS2 method = REML noclprint;
    class COUNTRG1(ref = "OTHER") AVISITN USUBJID;

    model CHG = COUNTRG1 AVISITN LOGBASE LOGBASE*AVISITN / DDFM = KR;

    repeated AVISITN / type=UN subject=USUBJID;

    lsmestimate AVISITN 'Change from Baseline in Weekly Attacks: Weeks 1-4'
                [1, 1] [1, 2] [1, 3] [1, 4]/ divisor = 4;

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
Trial flow chart

Trial flow chart

Table 4 Trial Procedures and Assessments

Visit Name	Screening Period	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	Completion	Safety Follow-up [c]	Withdrawal [d]
Visit Number	**1[a, z]**	**2[a]**	**3[b]**	**4[b]**	**5[a]**	**6[b]**	**7[b]**	**8[a]**	**9[b]**	**10[b]**	**11[a]**	**12[b]**	**13[b]**	**14[a]**	**15[a]**	**WD[a]**
End of Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**56**	
Visit Window [e] (days relative to nominal visit)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	
Screening and Baseline Procedures and Assessments																
Signed informed consent(s) [f, z]	√															
Demographics (age, sex, race)	√															
Diagnosis	√															
Disease-specific history [g]	√															
Relevant history (social, medical, psychiatric, neurological)	√															
Previous cluster headache abortive, transitional and preventive therapy use [g]	√															
Recent medication (past 3 months)	√															
Substance use (for example smoking and alcohol)	√															
Height	√															
Family history of cluster headache	√															
Urine drug screen	√															
Inclusion/exclusion criteria	√	√														
Efficacy Assessments (ePROs) [h, i]																
eDiary recording [j, k]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
eDiary compliance check [l]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
PGIC [k]			√	√	√	√	√	√	√	√	√	√	√	√		√

Visit Name	**Screening Period**	**IMP**	**Phone contact**	**Phone contact**	**IMP**	**Phone contact**	**Phone contact**	**IMP**	**Phone contact**	**Phone contact**	**IMP**	**Phone contact**	**Phone contact**	**Completion**	**Safety Follow-up [c]**	**Withdrawal [d]**
Visit Number	**1[a, z]**	**2[a]**	**3[b]**	**4[b]**	**5[a]**	**6[b]**	**7[b]**	**8[a]**	**9[b]**	**10[b]**	**11[a]**	**12[b]**	**13[b]**	**14[a]**	**15[a]**	**WD[a]**
End of Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**56**	
Visit Window [e] (days relative to nominal visit)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	
SIS [k]		√	√		√	√		√	√		√	√		√		√
Pharmacoeconomic Assessments (ePROs) [h, i]																
EQ-5D-5L [k]		√	√			√			√			√		√		√
HCRU [k]		√	√			√			√			√		√		√
WPAI:GH2.0 [k]		√	√			√			√			√		√		√
Pharmacokinetic Assessments																
Blood sampling for exploratory eptinezumab quantification [m, s]		√			√			√			√			√	√	√
Pharmacodynamic Assessments (exploratory biomarkers)																
Blood sampling for pharmacodynamic/exploratory biomarkers [m, s]		√			√			√			√			√		√
Safety Assessments																
Adverse events [n, o, y]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Blood and urine sampling for clinical safety laboratory tests [n]	√	√			√			√			√			√	√	√
Blood sampling for ADA including NAbs [n, u]		√			√			√			√			√	√	√
Vital signs [n, o] (including body temperature), weight	√	√			√			√			√			√	√	√
ECG [n]	√	√			√			√			√			√	√	√
Examinations (physical, neurological) [p]	√	√			√			√			√			√	√	√
C-SSRS [n, q]	√	√			√			√			√			√	√	√
Biobanking [r]																
Blood sampling for gene expression profiling (RNA) [s]		√						√						√		

Visit Name	Screening Period	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	IMP	Phone contact	Phone contact	Completion	Safety Follow-up [c]	Withdrawal [d]
Visit Number	**1[a, z]**	**2[a]**	**3[b]**	**4[b]**	**5[a]**	**6[b]**	**7[b]**	**8[a]**	**9[b]**	**10[b]**	**11[a]**	**12[b]**	**13[b]**	**14[a]**	**15[a]**	**WD[a]**
End of Week	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**56**	
Visit Window [e] (days relative to nominal visit)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	
Blood sampling for metabolomics/proteomics (plasma) [s]		√						√						√		
Blood sampling for pharmacogenetics (DNA) (optional) [t]		√														
Blood sampling for possible future ADA assessment [u]		√			√			√			√			√	√	
Other Trial Procedures and Assessments																
IMP administered (IV infusion) [v]		√			√			√			√					
IMP accountability		√			√			√			√					
Concomitant medication (prescription and non-prescription) [n]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
eDiary training [i]	√															
ePRO training [i]	√															
eDiary closeout [w]														√		√
Pregnancy test [n, x]	√	√			√			√			√				√	√

ADA = anti-drug antibody; C-SSRS = Columbia-Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = EuroQol 5-Dimension 5-Level; HCRU = Health Care Resources Utilization; IMP = investigational medicinal product; IV = intravenous; NAbs = neutralizing antibodies; PGIC = Patient Global Impression of Change; ePRO = electronic participant-reported outcome; RNA = ribonucleic acid; SIS = Sleep Impact Scale; WD = Withdrawal; WPAI:GH2.0 = Work Productivity Activity Impairment: General Health second version.

a This visit should be a site visit.

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

c The SFU Visit should be scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

d Participants who withdraw from study, 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 2).

f At the Screening Visit, the participant will be asked to sign the main Informed Consent Form (ICF), and the ICF for blood sampling for pharmacogenetics (optional). Depending of the country requirements, the number of ICFs may be different. Under exceptional circumstances, the discussion with the participants about the Informed Consent Form(s) can be done as a virtual clinic visit and the Informed Consent Form(s) can be provided remotely in line with the US FDA and EMA guidances. According to the EMA guidance, this could comprise contacting the participants via phone or video-calls and obtaining oral consents, to be documented in the participants' medical records, supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the participants are back at the clinical sites.

g Participants must have adequately documented records or reliable history of cCH and previous treatment for cCH within the 12 months prior to the Screening Visit. See protocol (section 12) for definition of adequately documented records.

h During the Treatment Period, ePROs which are scheduled in alignment with a clinic visit can be completed in the clinic or in the remote setting within 3 days 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 3 days prior to the scheduled phone contact date.

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

j Participants must complete the eDiary daily during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40) and weekly for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48.

k Participants must complete the daily eDiary and ePRO entries prior to infusion and prior to any interaction with the clinical site staff.

l In addition to the eDiary compliance checks performed at the defined trial visits, ongoing evaluation of eDiary compliance will be performed by the clinical site (based on eDiary reporting) and more frequent contact with participants may be performed in case of non-compliance.

m At IMP Visits, two blood samples will be collected for exploratory eptinezumab quantification and exploratory biomarkers – one sample prior to the eptinezumab infusion and one sample 1 hour after the end of the infusion.

n Infusion must be preceded by the assessment of vital signs (including body temperature), weight, concomitant medications, adverse events, ECG, blood sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), urine sampling (for clinical safety laboratory and pregnancy tests) and C-SSRS. Vital signs must be assessed prior to blood sampling.

o Vital signs (including body temperature) and adverse events must be checked both prior to and after infusion. Vital signs must be assessed prior to blood sampling.

p Physical and neurological examinations for all clinic visits after the Screening Visit are to be conducted at the discretion of the investigator. If these examinations are conducted at an IMP Visit, these must be performed prior to the infusion.

q C-SSRS will be administered by the authorised rater at the clinic.

r Biobank may be excluded or optional per local regulation.

s Exploratory gene expression profiling (ribonucleic acid [RNA]) and metabolomics/proteomics, including blood sampling for exploratory eptinezumab quantification, ADA biobanking and exploratory biomarkers, is covered by the main Informed Consent Form.

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

u Blood samples for safety ADA/NAb assessments and ADA biobanking (possible future analysis) will be drawn at Day 0/Visit 2, prior to the second eptinezumab infusion (Week 12/Visit 5), prior to the third eptinezumab infusion (Week 24/Visit 8), prior to the fourth eptinezumab infusion (Week 36/Visit 11), Completion Visit (Week 48/Visit 14), SFU Visit (Week 56/Visit 15). A Withdrawal Visit (if the participant withdraws) sample will only be drawn for the safety ADA/NAb assessments when applicable.

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

warranted.

w The eDiary closeout will take place at Completion Visit (Week 48/Visit 14) / Withdrawal Visit (for participants who withdraw). Details will be provided in a separate training module.

x For women of childbearing potential, pregnancy test at the Screening Visit and the SFU Visit is to be conducted using serum beta-human chorionic gonadotropin (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.

y Adverse events (serious and non-serious) must be collected, recorded, and reported to Lundbeck from the time the participant has signed the Informed Consent Form(s) at the Screening Visit. Pre-treatment adverse events will also be collected.

z The Screening Visit assessments may be extended over several days if needed. The date of the first assessment (except Informed Consent Form) should be entered in the electronic case report form (eCRF) as the visit date. eDiary must be provided to the participant on the date of that first assessment, which is considered as the first day of the 28-day Screening Period.

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 Trial Drug Infusion	Angioedema and urticaria (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Bronchial disorders (excl neoplasms) (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Infusion site reactions (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Oral soft tissue signs and symptoms (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Oral soft tissue swelling and oedema (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Pruritus NEC (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Rashes, eruptions and exanthems NEC (HLT) (primary PTs only)	TEAE on the day of dosing after the infusion was started or during the 7 days after dosing
	Respiratory disorders NEC (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Respiratory tract signs and symptoms (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started
	Upper respiratory tract disorders (excl infections) (HLGT) (primary PTs only)	TEAE on the day of dosing after the infusion was started

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