Statistical Analysis Plan

Interventional, randomized, double-blind, parallel-group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments

Eptinezumab

Study No.:	18898A
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
[redacted]	[redacted]
SAP date (v.1.0):	8 March 2021
SAP date (v.2.0):	13 October 2021

Table of Contents

Appendices

List of Panels and Tables

List of Abbreviations and Definitions of Terms

ANCOVA	analysis of covariance
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS_LT	all-patients-treated-long-term set
CI	confidence interval
CM	chronic migraine
CMH	Cochran-Mantel-Haenszel
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EM	episodic migraine
EQ-5D-5L	Euroqol 5 Dimensions
FAS	full-analysis set
FAS_LT	full-analysis-long-term set
HCRU	health care resource utilization
HIT-6	headache impact test
IMP	investigational medicinal product
MAR	missing at random
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MHDs	monthly headache days
ML	maximum likelihood
MMDs	monthly migraine days
MMRM	mixed model for repeated measurements
MNAR	missing not at random
MOH	medication overuse headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire Version 2.1
PCS	potentially clinically significant
REML	restricted maximum likelihood
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
WPAI:M	Work Productivity and Activity Impairment: Migraine

1 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 1.

Panel 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments	• Primary endpoint: - Change from baseline in the number of monthly migraine days (Weeks 1-12) • Key secondary endpoints: - Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 1-12) - Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 1-12) - Change from baseline in the number of monthly migraine days (Weeks 13-24) • Secondary endpoints: - Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 13-24) - Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 13-24) - Response: patients with 100% reduction from baseline in monthly migraine days (Weeks 1-12) - Response: patients with 50% reduction from baseline in monthly headache days (Weeks 1-12) - Response: patients with 75% reduction from baseline in monthly headache days (Weeks 1-12) - Response: patients with 100% reduction from baseline in monthly headache days (Weeks 1-12) - Change from baseline in the number of monthly headache days (Weeks 1-12) - Change from baseline in percentage of migraines/headaches with severe pain intensity (Weeks 1- 12) - Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 1-12) - Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 13-24) - Change from baseline in the number of monthly migraine days with use of acute medication (Weeks 1- 12) - Change from baseline in number of monthly migraine days with use of acute medication (Weeks 13-24) - Patient Global Impression of Change (PGIC) score at Week 12 - PGIC score at Week 24 - Change from baseline in the number of monthly migraine days in patients with Medication Overuse Headache (MOH) (Weeks 1-12) - Patients with a migraine on the day after first dosing - Most Bothersome Symptom (MBS) score at Week 12, as measured relative to Baseline

Objectives	Endpoints
	• Exploratory endpoints: - Change from baseline in the number of monthly headache episodes for each 12-week period - Change from baseline in the number of monthly migraine attacks for each 12-week period
Secondary Objectives • To evaluate the health-related quality of life and work productivity impact of eptinezumab	• Key secondary endpoints: - Change from baseline to Week 12 in the Headache Impact Test (HIT-6) score • Secondary endpoints: - Change from baseline to Week 24 in the HIT-6 score - Change from baseline to Week 12 in the Migraine-Specific Quality of Life (MSQ v2.1) sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function) - Change from baseline to Week 12 in the Health-Related Quality of Life (EQ-5D-5L) Visual Analogue Scale (VAS) score - Health Care Resources Utilization (HCRU) at Week 12 - Change from baseline to Week 24 in the MSQ v2.1 sub-scores - Change from baseline to Week 24 in the EQ-5D-5L VAS score - HCRU at Week 24 - Change from baseline to Week 12 in the Work Productivity and Activity Impairment questionnaire (WPAI) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) - Change from baseline to Week 24 in the WPAI sub-scores - Response: Patients with a 5-point reduction from baseline to Week 12 in HIT-6 score - Response: Patients with a 5-point reduction from baseline to Week 24 in HIT-6 score
• To evaluate the effect of long-term treatment with eptinezumab	• Secondary endpoints: - Change from baseline in the number of monthly migraine days (Weeks 25-36, 37-48, 49-60, 61-72) - Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 25-36, 37-48, 49-60, 61-72) - Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 25-36, 37-48, 49-60, 61-72) - Change from baseline in the HIT-6 score (at Weeks 36, 48, 60, and 72) • Exploratory endpoints: - Response: patients with 100% reduction from baseline in monthly migraine days - Response: patients with 50% reduction from baseline in monthly headache days - Response: patients with 75% reduction from baseline in monthly headache days - Response: patients with 100% reduction from baseline in monthly headache days - Change from baseline in percentage of migraines/headaches with severe pain intensity

Objectives	Endpoints
	- Change from baseline in the number of monthly days with use of acute migraine medication - Change from baseline in the number of monthly migraine days with use of acute migraine medication - PGIC score - Change from baseline in the number of monthly migraine days in patients with MOH - MBS score - Change from baseline in monthly number of Migraine attacks for each 12-week period - Change from baseline in monthly number of Headache episodes for each 12-week period - Change from baseline in the MSQ v2.1 sub-scores - Change from baseline in the EQ-5D-5L VAS score - HCRU - Change from baseline in the WPAI sub-scores
Safety Objective • To evaluate the safety and tolerability of eptinezumab • To evaluate the long-term safety and tolerability of eptinezumab	• Safety Endpoints - Adverse events - Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values - Potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values - Development of specific anti-eptinezumab antibodies (ADA) including neutralizing antibodies (NAbs) - Columbia-Suicide Severity Rating Scale (C-SSRS) score

2 Study Design

This is an interventional, multi-national, multi-site, randomized, double-blind, placebo-controlled Phase IIIb study designed to demonstrate efficacy and safety of eptinezumab for migraine prevention in patients with unsuccessful prior preventive treatments. The placebo-controlled period will be followed by an extension period where all patients will receive active treatment to assess the long-term safety, tolerability and effect of eptinezumab.

The target population for this study is defined as patients with chronic migraine (CM) or episodic migraine (EM), as outlined in the IHS ICHD-3 guidelines[1] with documented evidence of migraine occurring on ≥4 days per month prior to screening as confirmed via prospectively collected information in the eDiary during the Screening Period, and with documented evidence of failure to 2-4 different preventive migraine medications in the past 10 years. The aim is that approximately 40% of the randomized patients are patients with EM.

It is planned that 840 patients will be randomly allocated to one of three treatment groups: eptinezumab 300 mg, eptinezumab 100 mg, or placebo, in a ratio of 1:1:1.

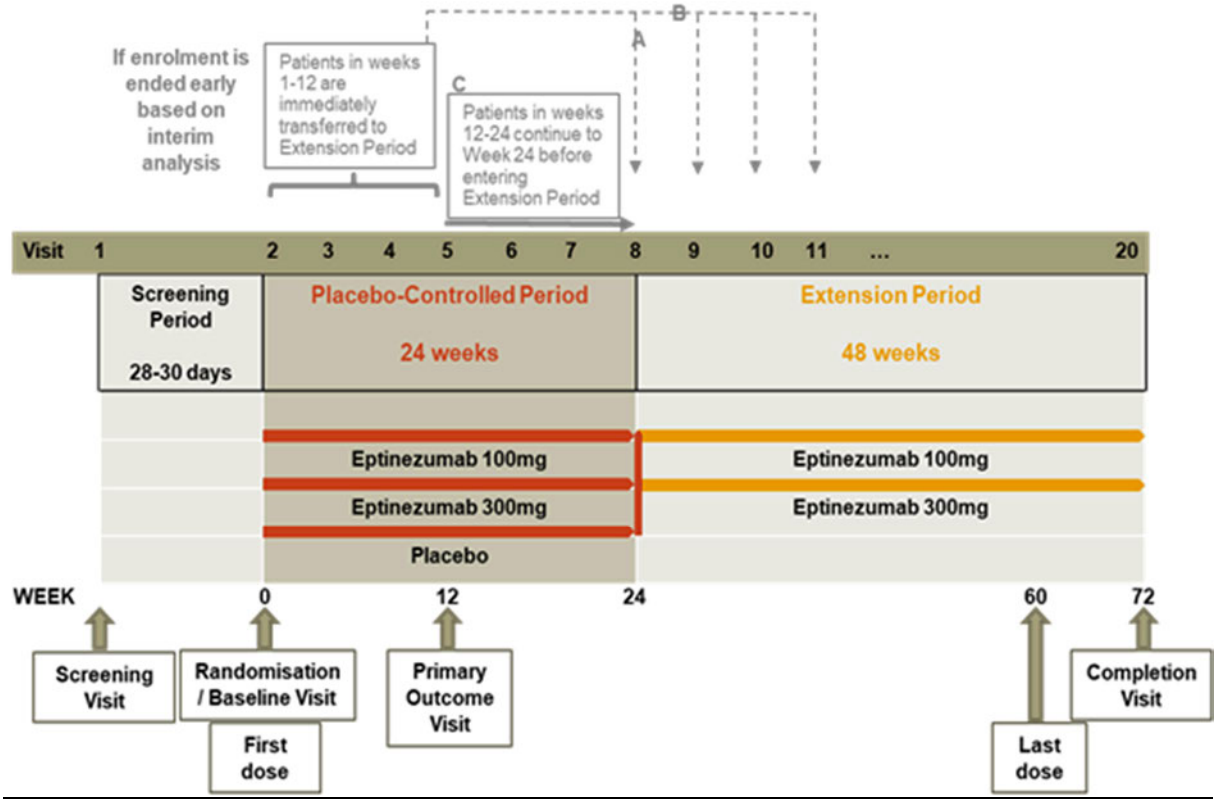
Randomization will be stratified by country and monthly headache days (MHDs) at baseline (≤14 MHDs/ >14 MHDs).

The patient will receive IMP starting from the Baseline Visit to follow a dosing schedule with IV infusions every 12 weeks with either eptinezumab or placebo over 30 minutes (+15).

At Visit 8 patients will enter the Extension Period. Patients who were assigned to placebo in the Placebo-controlled Period will be randomly allocated to one of two treatment groups: eptinezumab 300 mg or eptinezumab 100 mg with a ratio of 1:1. Patients assigned to eptinezumab 300 mg or eptinezumab 100 mg in the Placebo-controlled Period will continue on their original assignments.

An overview of the study is presented in Panel 2 and the scheduled study procedures and assessments are summarized in Appendix II. See also the *Clinical Study Protocol* for further details on the study design.

Panel 2 Study Design



For patients who withdraw, except for those who withdraw their consent, a Withdrawal Visit will be scheduled 12 weeks after the last dose of IMP. The withdrawal visit will include Safety Follow-up evaluations and will therefore also serve as a Safety Follow-up Visit.

For patients who withdraw prior to Week 24 the Withdrawal Visit will allow for eDiary closeout and for a final assessment of scales not based on the eDiary. Patients are expected to complete their eDiary until this Withdrawal Visit unless the patient withdraws consent.

2.1 Clinical Study Report

The data collected in the Placebo-controlled Period will be used for generating the output to be included in the *Clinical Study Report* (CSR). Upon completion of the study, an addendum to the *Clinical Study Report*, including the results from the Extension Period, will be produced.

This means that all tables, listings, and figures that are related to the Extension Period or cover the full study period will be prepared after the *Clinical Study Report* for the study is final. This *Statistical Analysis Plan* describes both the output that will be prepared for the *Clinical Study Report* and for the addendum.

Throughout this document, the term *CSR* will be used to refer to the *Clinical Study Report* including the output from the Placebo-controlled Period and the term *addendum to CSR* will be used to refer to the addendum that includes the results from the Extension Period.

3 COVID-19

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

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

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

Specific output addressing the impact of COVID-19 for this trial is specified in Sections 7.1 and 7.2.

4 Definitions

4.1 Definition of Periods

The study consists of the following periods:

- *Screening Period* (28-30 days): Starts at the Screening Visit and continues up to start of Visit 2 IMP infusion
- *Placebo-Controlled Period*: Starts at start of Visit 2 IMP infusion and continues up to start of Visit 8 IMP infusion
- *Extension Period*: Starts at start of Visit 8 IMP infusion and continues up to and including Visit 20

4.2 Definition of Baseline

For migraine and headache endpoints, the baseline value will be based upon the data recorded in the headache eDiary during the first 28 days following screening.

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

4.3 Definition of Withdrawal

The group of patients who withdrew in the Placebo-controlled Period before receiving any IMP in the Extension period will be described as *withdrawn* in the Placebo-controlled Period. The complementary group will be described as *completed* in the Placebo-controlled Period.

Similarly, for the Extension Period the group of patients who withdrew after receiving IMP in the Extension Period will be described as *withdrawn* in the Extension Period and the complementary group will be described as *completed* in the Extension Period.

4.4 Definition of Planned versus Actual Treatment

Every 12 weeks, patients will receive either eptinezumab 300 mg, eptinezumab 100 mg, or placebo in the Placebo-controlled Period and either eptinezumab 300 mg or eptinezumab 100 mg in the Extension Period.

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

Actual treatment is defined as the treatment a patient actually received during the study. If a patient received a different dose than what was planned at a given visit, the actual treatment in the relevant Period will equal the highest dose received. The actual treatment group will be determined separately for the Placebo-controlled Period and the Extension Period.

The term *treatment sequence* will be used to denote the treatment groups arising by combining the treatments received in the Placebo-controlled Period and the treatments received in the Extension Period, i.e. if all patients receive their treatment as planned the 4 groups are: Placebo-eptinezumab 100 mg, placebo-eptinezumab 300 mg, eptinezumab 100 mg-eptinezumab 100 mg, and eptinezumab 300 mg-eptinezumab 300 mg.

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

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

And the following will be summarized by actual treatment:

- Adverse events
- Exposure
- Disposition
- Laboratory parameters, vital signs, ECG, and C-SSRS

Unless otherwise specified, data listings will display actual treatment.

4.5 Definition of Migraine and Headache Days

For the purpose of endpoint derivations, the following definitions of migraine and headache days will be used. The definition of a migraine day reflects the strategy chosen to handle the intercurrent event of using acute migraine medication in the primary estimand, as outlined in Sections 12.3.1 and 12.3.3.

In this document, the term headache will encompass both headaches and migraine headaches. Migraine headaches (henceforth simply referred to as "migraines") are a subgroup of headaches with characteristics outlined below (Section 4.5.1). Using this definition, we have that all migraines are headaches but not all headaches are migraines.

Headaches will be self-reported by the patient using an electronic headache diary (eDiary). The eDiary is split into two parts, the headache diary and the evening diary. The headache diary is the part of the eDiary where the start and stop date and times of experienced headaches are recorded along with headache characteristics used for classifying headaches as migraines, and the evening diary is the part of the eDiary that patients are expected to complete each day during the study regardless of whether or not they experienced a headache on that day.

Randomization is stratified by Monthly Headache Days (MHDs) at baseline (≤14 MHDs/ >14 MHDs). The stratum is based on a calculation performed directly in the eDiary at Baseline. The eDiary uses an algorithm described in the Project Design Specification (PDS), a document providing the technical specifications for the set-up of the eDiary, for determining whether a day in the screening period classifies as a day with a headache or a day with a migraine. Patients are deemed eligible if, according to this algorithm, they fall into the criteria for CM or EM as defined in inclusion criterion 10 in the *Clinical Study Protocol* (ed. 1.0 and 2.0), i.e:

- For patients with CM: Migraine occurring on ≥8 days and headache occurring on >14 days.
- For patients with EM: Migraine occurring on ≥4 days and headache occurring on ≤14 days

In this document, whenever stratum or stratification factor is mentioned, the reference is to this classification into EM and CM that was used for randomization.

The PDS definition of a migraine day can be seen in Appendix III.

4.5.1 Migraine Day

A migraine day is defined as any day with a headache that meets criteria A, B, C or D listed below:

A. All of the following criteria:
1. Lasted 4 hours or more
2. Had at least 2 of the following:
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe pain intensity
   d. Aggravation by or causing avoidance of routine physical activity
3. Had at least 1 of the following:
   a. Nausea
   b. Vomiting
   c. Photophobia **and** phonophobia

B. A headache that lasted 30 minutes or more and patient had an aura with the headache

C. A headache that lasted 30 minutes or more and met 2 of the 3 following criteria:
1. Lasted 4 hours or more
2. Had at least 2 of the following:
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe pain intensity
   d. Aggravation by or causing avoidance of routine physical activity
3. Had at least 1 of the following:
   a. Nausea
   b. Vomiting
   c. Photophobia and phonophobia

D. Patient took medication to treat the headache because they believed they were having a migraine

4.5.2 Headache Day

A headache day is defined as any day with a headache that meets one of the following criteria:
- Lasted 30 minutes or more
- Meets the criteria for being a migraine, i.e. fulfils either criteria A, B, C or D above (see Section 4.5.1)

5 Analysis Sets

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

- *all-patients-randomized set* (APRS) – all randomized patients
- *all-patients-treated set* (APTS) – all patients in the APRS who received at least one infusion of the double-blind IMP
- *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
- *all-patients-treated-long-term* set (APTS_LT) – all patients in the APRS who received at least one infusion of IMP and had a visit in the Extension Period
- *full-analysis-long-term set* (FAS_LT) – all patients in the APTS_LT who had a valid baseline assessment and a valid assessment of monthly migraine days in the Extension Period

The patients and data will be classified into the analysis sets according to these definitions at separate *Classification Meetings*:

- For the reporting of the Placebo-controlled Period, the Classification meeting will be held after the data base release for the reporting of the Placebo-controlled Period but before the blind has been broken and will concern the classification into APTS and FAS.
- For the *addendum to CSR*, the Classification meeting will be held after the data base release for the reporting of the Extension Period and will concern the classification into APTS_LT and FAS_LT.

Efficacy analyses of the Placebo-controlled Period will be based on FAS, and efficacy analyses in the Extension Period will be based on FAS_LT.

Safety tables (including exposure and concomitant medications) will be based on APTS in the Placebo-controlled Period and APTS_LT in the Extension Period.

6 Descriptive Statistics

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

Unless otherwise specified, data listings for the Placebo-controlled Period will include site, treatment group, patient screening number, sex, age, race, and baseline weight. For the Extension Period, the listings will include both treatment group in the Placebo-controlled Period and treatment group in the Extension Period in addition to the variables included in listings for the Placebo-controlled Period.

7 Patient Disposition

7.1 Summary of Patient Disposition

Patient disposition will be summarized separately for the Placebo-controlled Period and the Extension Period and will present patient disposition overall and by treatment group. If needed, further tables summarizing disposition by country or site and treatment group can be added.

The summaries for the Placebo-controlled Period will include the number of patients included in APRS, APTS, and FAS, and the number of patients within APTS, who completed or withdrew, as well as the number of screened patients and number of screening failures.

The summaries for the Extension Period will include the number of patients included in APTS_LT and FAS_LT and the number of patients within APTS_LT, who completed or withdrew.

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

7.2 Withdrawals

For each period, the number of patients who withdrew from treatment, which also implies that they withdrew from the study, will be summarized by treatment group, and primary reason for withdrawal, and by treatment group and all reasons for withdrawal.

Patients who withdrew will be listed for each period. The listings will include the number of days in the study until withdrawal, the date of first IMP infusion, the date of the latest IMP infusion prior to withdrawal, the number of days since latest IMP infusion, the primary reason for withdrawal, all reasons for withdrawal, specification of 'Other' reason, and a flag if the drug code was broken. For the listing for the Extension Period both date of first IMP in the Placebo-controlled Period and date of first IMP in the Extension Period will be included.

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

If relevant, Kaplan-Meier failure plots of time to withdrawal in each period will be presented by treatment group. The time will be calculated from the date of first dose of IMP in the period to the date of completion or withdrawal. Patients who completed the period will be regarded as censored. For the Extension Period, the plot will be by treatment sequence group.

All tables, graphs, and listings will be based on the APTS for the Placebo-controlled Period and on APTS_LT for the Extension Period.

8 Demographics and Baseline Characteristics

Demographics (sex, age, age group, race, ethnicity, region, country); baseline characteristics (height, weight, and BMI); baseline disease characteristics; and baseline efficacy variables will be summarized for the Placebo-controlled Period by treatment group.

The disease characteristics comprise of age and age group (≤ 21 years, > 21 years) at first diagnosis of migraine, duration and duration group (≤ 15 years, > 15 years) of first migraine diagnosis at baseline, whether the current diagnosis is a CM or EM diagnosis, duration of current CM/EM diagnosis, whether the patient suffers from fully reversible aura symptoms and if yes, which aura symptoms, whether the patient experiences aura symptoms without headache and if yes, which aura symptoms, whether the patient has an MOH diagnosis, for women whether migraines started before or after menarche and for men whether migraines started before or after puberty, and whether the start of migraine was related to any event.

The baseline efficacy variables that will be summarized will be split into eDiary reported baseline migraine characteristics and other efficacy variables.

The eDiary reported baseline migraine characteristics that will be summarized are the number of baseline MMDs, number of baseline MHDs, number of monthly migraine attacks and headache episodes at baseline, percentage of headaches and migraines with severe pain intensity, baseline average length of migraine attacks and headache episodes, number of baseline MMDs with use of acute medication, and number of monthly days with use of acute medication, which are all collected during the screening period. The number of patients in each stratum based on the definition in Appendix III will also be included, as well as the number of EM/CM patients and low/high frequency EM patients (see Section 12.3.7) based on baseline MMDs and MHDs derived according to the definitions in Section 4.5 and the descriptions in Section 19.1.1.1.

The other baseline efficacy variables that will be summarized are HIT-6 total score – both summarized as a continuous variable and as a categorical displaying the percentage and counts of the life impact categories (see Section 19.1.4) – MSQ v2.1 sub-scores, EQ-5D-5L VAS score, WPAI sub-scores, and counts and percentages of MBS symptom chosen at screening.

Concurrent as well as relevant past medical, neurological, and psychiatric disorders will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA , Version 23.0 or later) and summarized by treatment group. Social history will be summarized by treatment group.

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.

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

9 Recent and Concomitant Medication

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

Medications will be classified according to the start and stop dates and summarized by anatomical therapeutic chemical (ATC) code level 4, generic drug name, treatment group, and period. Handling of missing or incomplete dates is specified in Section 19.3.4.

The following categories will be used:

- Prior: Medications with a stop date before first IMP infusion.
- Concomitant Placebo-controlled Period: Medications with a start date at or after the date of first IMP infusion and prior to the date of V8 IMP infusion, medications with a stop date at or after the date of first IMP infusion that also have a start date prior to the date of V8 IMP infusion, and medications where both start and stop date are completely missing. Ongoing medications with a start date prior to the date of V8 IMP infusion are also included, as well as medications with a start date prior to the date of V8 IMP infusion with a completely missing stop date.
- Concomitant Extension Period: Medications with a start or stop date at or after the date of V8 IMP infusion and medications where both start and stop date are completely missing. Ongoing medications are also included, as well as medications with a completely missing stop date.

The tables for the Placebo-controlled Period will be based on the APTS and the tables for the Extension Period will be based on APTS_LT.

The summaries will be repeated for prophylactic and acute migraine medications, which will be identified via a clinical review of the coded medication data.

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

A similar listing will be provided for the patients taking disallowed concomitant medications in the Extension Period based on the APTS_LT for inclusion in the *addendum to CSR*.

The eDiary reported medications will be handled separately. In the evening eDiary, patients are asked each day to fill out whether they used any of the following medications during that day: Ergotamine, triptan, analgesic, opioid, or combination analgesic. The number of patients taking each of the medication types will be presented for each 4-week interval in the study by treatment group, separately for the Placebo-controlled Period and the Extension Period.

9.1 Documented Evidence of Treatment Failure

Summaries of prior preventive treatment failure medications will be presented for the Placebo-controlled Period by treatment group. The number and percentage of patients, who experienced each type of treatment failure (lack of efficacy, safety/tolerability, or contraindication) will also be presented by treatment group, as well as the number of prior preventive treatment failures.

The number and percentage of patients fulfilling criteria for inclusion into AMNOG subpopulation B (defined October 2020), henceforth referred to as *subpopulation B*, will be summarized.

Patients fulfilling criteria for *subpopulation B* will be defined as patients who have at least 2 documented treatment failures due to inadequate efficacy or poor tolerability of either:

- metoprolol or propranolol
- flunarizine
- topiramate
- amitriptyline

The summaries will be based on the APTS.

10 Exposure

For each period, the total number of infusions received and total number of infusions completed as planned will be summarized by treatment group.

Furthermore, for each infusion visit, the number of infusions received, completed as planned, temporarily interrupted, and lasted longer than 30(+15) minutes, as well as descriptive statistics for the duration of infusions and duration of temporary interruptions will be summarized by treatment group.

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

In addition, all infusion data will be listed for each period separately.

For the Placebo-controlled Period, the tables and listings will be made based on APTS and for the Extension Period, the tables and listings will be made based on APTS_LT. For the Extension Period, the summaries will be by treatment sequence group.

11 eDiary Compliance

For each period, the rate of days where the eDiary has been missed within each 4-week interval will be summarized and presented by 4-week interval and treatment group.

Furthermore, the number of patients missing 7 days or more and 14 days or more in a 28-day period will be presented by 4-week interval and treatment group, separately for each period.

A day where the eDiary has been missed is defined as a day where the subject did not fill out anything in the evening eDiary and did not have a headache reported in the headache eDiary.

The summaries will be based on the APTS for the Placebo-controlled Period and on the APTS_LT for the Extension Period.

12 Efficacy

12.1 General Efficacy Analysis Methodology

Unless otherwise specified, all the efficacy analyses for the Placebo-controlled Period will be based on the FAS and all the efficacy analyses for the Extension Period will be based on the FAS_LT.

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

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

12.2 Testing Strategy

The testing strategy will be a sequence of tests, either testing one endpoint at a time or using Bonferroni-Holm to test a group of endpoints. Only if one step has shown a statistically significant effect will the formal testing continue with the next step, thus ensuring protection of the type 1 error. The steps are described below. A graphical representation of the testing strategy can be found in Panel 3.

A significance level of 0.05 will be used. The significance level is denoted by α below.

Step 1
Test the primary endpoint change from baseline in MMDs (Weeks 1-12) for the 300 mg dose compared to placebo on a significance level of α. Only if the p-value <α in favour of the 300 mg dose is the effect considered statistically significant and the testing continues with the next step.

Step 2
Test the key secondary endpoint 50% responders for MMD (Weeks 1-12) for the 300 mg dose compared to placebo, using a significance level of α. Only if the p-value <α in favour of the 300 mg dose is the effect considered statistically significant and the testing continues with the next step.

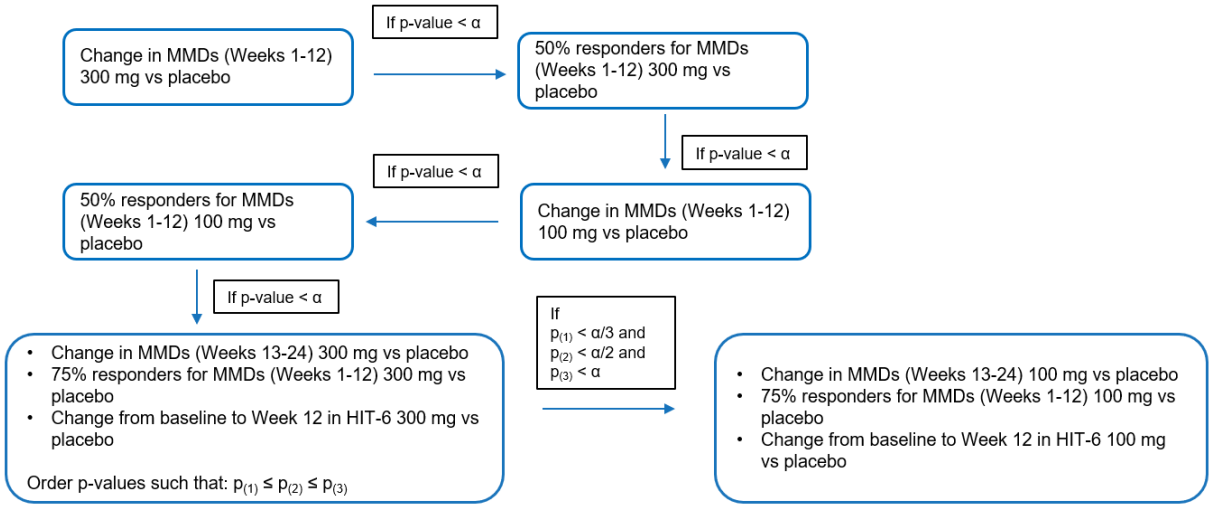
Step 3
Test the primary endpoint change from baseline in MMDs (Weeks 1-12) for the 100 mg dose compared to placebo on a significance level of α. Only if the p-value <α in favour of the 100 mg dose is the effect considered statistically significant and the testing continues with the next step.

Step 4
Test the key secondary endpoint 50% responders for MMD (Weeks 1-12) for the 100 mg dose compared to placebo, using a significance level of α. Only if the p-value <α in favour of the 100 mg dose is the effect considered statistically significant and the testing continues with the next step.

Step 5
Uses Bonferroni-Holm to test the 3 key secondary endpoints: Change from baseline in MMDs (Weeks 13-24), 75% responders for MMD (Weeks 1-12), Change from baseline to Week 12 in HIT-6. All comparisons are of the 300 mg dose compared to placebo. If the smallest of the 3 p-values is <α /3 in favour of the 300 mg dose then the effect seen on this endpoint is considered statistically significant, and the testing continues. Next, if the second smallest p-value is <α/2 in favour of the 300 mg dose, then the effect seen on this endpoint is considered statistically significant, and the testing continues. If the largest p-value is <α in favour of the 300 mg dose then the effect seen on this endpoint is considered statistically significant, and the testing continues.

Step 6
Uses Bonferroni-Holm to test the 3 key secondary endpoints: Change from baseline in MMDs (Weeks 13-24), 75% responders for MMD (Weeks 1-12), Change from baseline to Week 12 in HIT-6. All comparisons are of the 100 mg dose compared to placebo. If the smallest of the 3 p-values is <α /3 in favour of the 100 mg dose, then the effect seen on this endpoint is considered statistically significant, and the testing continues. Next, if the second smallest p-value is <α/2 in favour of the 100 mg dose, then the effect seen on this endpoint is considered statistically significant, and the testing continues. If the largest p-value is <α in favour of the 100 mg dose then, the effect seen on this endpoint is considered statistically significant.

Panel 3 Testing Strategy



12.3 Analysis Methodology for the Primary Endpoint

12.3.1 Primary Estimand

A summary of the intercurrent events that will be addressed and the estimand attributes can be found below. Further details on the intercurrent events and the strategies used to address them are given in Section 12.3.3.

The primary estimand will be the effect of eptinezumab on number of monthly migraine days that would be seen in the hypothetical case where no acute medication was available, if patients withdrawing due to lack of efficacy remained on their current trajectory, if patients withdrawing due to adverse events at an early stage were considered as obtaining only limited improvement to their baseline disease level, and if the effect was considered regardless of use of preventive medication and infusion interruptions or terminations.

Intercurrent events that will be addressed:

- Use of acute medication to treat a headache
- Use of preventive migraine medication
- Withdrawal due to lack of efficacy
- Withdrawal due to adverse event
- Withdrawal due to other reasons
- Interruption/termination of infusions

Attributes of the primary estimand:

- The **treatment** condition of interest is eptinezumab (both 300 mg and 100 mg) compared to placebo

- The **population** is all patients that fulfil the inclusion and none of the exclusion criteria for the study
- The **endpoint** to be considered is the change from baseline in MMDs across weeks 1-12
- The **population-level summary** is the least squares mean difference between eptinezumab and placebo for the endpoint

12.3.2 Primary Analysis of the Primary Endpoint

Changes from Baseline in MMDs at the 6 first 4-week intervals will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The analysis will be performed using all available monthly scores for the first 6 months in the study derived as specified in Section 19.1.1. Below, the term "month" refers to 4-week periods.

The model will include the following fixed effects: month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, and Weeks 21-24), country, stratification factor (MHDs at baseline: ≤14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction. An unstructured variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following variance structures will be tried out, in the following order: first-order ante-dependence, heterogenous compound symmetry, compound symmetry, and the first to converge will be applied. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The SAS® code for the primary analysis is shown in Appendix IV.

The mean differences between each dose of eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-month interaction in the MMRM model. The estimates will be presented with p-values and 95% CIs. The primary comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 1-12. These averaged contrasts are obtained by weighting together the first 3 monthly least squares mean estimates for each dose. More specifically, they are computed via the matrix product: $kL\hat{\beta}$, where L is the $18\times p$ coefficient matrix used for computing the least squares mean estimates for the treatment-by-month interaction effects, $\hat{\beta}$ is the $p\times 1$ vector of parameter estimates, and k is a 1×18 vector of coefficients, which for the comparison between eptinezumab 100 mg and placebo is defined as:

$$k = \left(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}, 0_9, -\frac{1}{3}, -\frac{1}{3}, -\frac{1}{3}, 0_3\right),$$

and for the comparison between eptinezumab 300 mg and placebo is defined as:

$$k = \left(0_6, \frac{1}{3}, \frac{1}{3}, \frac{1}{3}, 0_3, -\frac{1}{3}, -\frac{1}{3}, -\frac{1}{3}, 0_3\right),$$

where 0_x is used to represent a vector consisting of x 0's, and it is assumed that the ordering of the levels of the treatment factor is: 100 mg, 300 mg, placebo and the ordering of the levels

of the month factor is: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, and Weeks 21-24.

The primary comparisons will be part of the testing strategy described in section 12.2.

12.3.3 Strategies for Addressing Intercurrent Events in Primary Estimand

Use of acute medication to treat a headache
When patients complete a headache in the headache eDiary they are asked whether they took any medications to treat the headache. In case of an affirmative answer, they are asked the question "*Did you take this medication because you believed that you were having a migraine?*". In a hypothetical scenario where medication is not available, it is hypothesised that patients that answer this question with a "*Yes*" would have experienced a migraine.

Thereby, a hypothetical strategy is used to address the intercurrent event of use of acute medication by counting a day where patients took medication because they believed they were experiencing a migraine as a migraine day, using the definition given in Section 4.5.1.

Use of preventive migraine medication
Initiating a new preventive migraine treatment and concomitant use of preventive migraine treatment at study entry is generally disallowed in the study, see the *Clinical Study Protocol*, Appendix II.

A treatment policy strategy is used to address the intercurrent event of use of preventive migraine medication by using the data collected regardless of whether or not the patient uses preventive migraine treatment.

Withdrawal due to lack of efficacy
It is hypothesised that patients withdrawing due to lack of efficacy will remain on their current level of MMDs after withdrawing at least until 12 weeks after their first dose.

Therefore, the intercurrent event of experiencing lack of efficacy resulting in a patient withdrawing, will be addressed using a hypothetical strategy. In the hypothetical world where patients would not drop out due to lack of efficacy, it is hypothesised that the patients would continue on their current unsatisfactory symptom level, so imputation of missing data in this situation aim to ensure that the current symptom level is used for the analysis even if very little data is available. See details of the implementation in the rules for handling missing data described in Section 19.1.1.

Withdrawal due to adverse event
It is hypothesised that patients withdrawing very early in the study (during the first 4 weeks after first IMP infusion) due to adverse events have not been successfully treated. Therefore, in a situation where a patient withdraws during the first 4 weeks after first IMP infusion and the amount of data collected through the eDiary is not sufficient to derive a monthly score using the general derivation rules, the missing data is penalized to reflect that the symptom level will be close to the expected higher level of MMDs that was experienced at Baseline.

Patients withdrawing due to adverse events later in the study are hypothesised to behave similarly to the study population as a whole.

Details of the imputations used can be seen in the rules for handling missing data described in Section 19.1.1.

Withdrawal due to other reasons
Withdrawals due to other reasons than lack of efficacy or adverse events will be handled with a treatment policy strategy using the data collected regardless of the intercurrent event and using the imputation rules specified in Section 19.1.1.

Interruption/termination of infusions
If interruption or termination of infusion leads to withdrawal, it is handled according to the rules above.

Temporary interruption of infusion is not expected to impact the efficacy data. Premature termination of infusion (that is, only receiving a partial infusion) could impact the efficacy. However, it is expected that the implications of a partial infusion will be reflected in the collected eDiary data.

Hence, the intercurrent events of temporary infusion interruptions, premature terminations of infusions, and complete termination of infusions not leading to withdrawal will be addressed using a treatment policy strategy by using the data collected regardless of these intercurrent events.

12.3.4 Rationale for Selected Analysis Method for the Primary Endpoint

The MMDs are considered continuous data, and they are analysed using methods based on observations following a normal distribution. Given the repeated observation of normally distributed data, an MMRM analysis using all available data has been chosen for the primary analysis. Covariates are included in the model based on an approach including key factors representing study design features (month, treatment, MHD stratum, country), and baseline MMD score to account for differences in baseline MMDs and its predictive ability. When the MMRM analysis includes the individual factors mentioned as well as interaction of month and treatment, month and baseline score, and month and stratum, and applies an unstructured covariance, as described in Section 12.3.1, it allows for flexibility in modelling the development over time and similarly provides robust estimation, even under some deviation from the assumption of normality.

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

12.3.5 Sensitivity Analyses of the Primary Endpoint

Imputations for Withdrawals Due to Adverse Event or Lack of Efficacy

To explore the assumptions related to how patients withdrawing due to adverse events or lack of efficacy are behaving, an analysis similar to the primary analysis will be conducted, where monthly values for all patients are calculated using the *prorating* imputation rule described in Section 19.1.1.1 without penalization for early withdrawal due to adverse events or lack of efficacy as was done for the primary estimand. This means that the number of MMDs for all patients will be calculated according to rows 1-3 in Panel 5, even if patients are withdrawing due to lack of efficacy or adverse events.

Imputation for Weeks 1-4

To explore the robustness of the results to missing eDiary data in the first 4 weeks after infusion, an analysis similar to the primary analysis will be conducted, where monthly values in the first 4 weeks after first infusion are calculated using the *weighting* rule described in Section 19.1.1.1 if patients have less than 14 days with eDiary reporting in this period. This means that baseline values will be used in the calculation of Weeks 1-4 values for patients with less than 14 days of eDiary data in the 4 weeks after first infusion.

12.3.6 Supplementary Analyses of the Primary Endpoint

To provide additional insight into the understanding of the treatment effect, a supplementary analysis for the primary estimand will be conducted.

The supplementary analysis will be a repetition of the primary analysis for the change from baseline in number of MMDs but without differentiating between headaches where patients took medication to treat their headache and headaches where patients took medication to treat their headache because they believed they were having a migraine. This means that a day will be counted as a migraine day by changing criterion D in Section 4.5.1 to:

- Patient took medication to treat the headache.

12.3.7 Covariate Investigation and Subgroup Analyses of the Primary Endpoint

Subgroup analyses will be performed, where relevant, using the model specified in Section 12.3.2 on the set of patients included in the subgroup. For EM/CM and low/high frequency EM and CM (see below), the terms with stratum will be excluded from the model.

The subgroups that will be investigated are

- Sex
- Race: White and other
- EM (MMDs $\geq$ 4, MHDs $\leq$ 14) and CM (MMDs $\geq$ 8, MHDs >14) (based on baseline MMDs and MHDs derived according to the definitions in Section 4.5 and the descriptions in Section 19.1.1.1)
- Age group: $\leq$ 35 years and >35 years

- Medication overuse headache diagnosis
- Number of failed previous treatments (2 and > 2)
- Low frequency EM (4 ≤ MMDs < 8), high frequency EM (8 ≤ MMDs ≤ 14), and CM (MMDs ≥ 8) based on baseline MMDs and MHDs derived according to the definitions in Section 4.5 and the descriptions in Section 19.1.1.1.

The assumption of equal treatment effect across subgroups will be investigated on an exploratory basis for all subgroups listed above by adding the three-way interaction term subgroup-by-treatment-by-week to the model. A test for whether the 3-way interaction term and the 2-way interaction (subgroup-by-treatment) term can be removed from the model will be performed by comparing the model without both the 3-way interaction term and the subgroup-by-treatment 2-way interaction term to the model with the 3-way interaction term. This will be done by fitting both models using (maximum likelihood) ML and making a likelihood ratio test comparing -2*log(Q) to the asymptotic X^2 distribution, where Q is the quotient of the maximised likelihood functions. The p-value for this test will be reported.

12.4 Analysis Methodology for the Key Secondary Endpoints

12.4.1 Key Secondary Estimands

The key secondary endpoints 50% response (Weeks 1-12), 75% response (Weeks 1-12), and change from baseline in MMDs (Weeks 13-24) are all derived based on the number of MMDs for the relevant intervals.

Therefore, the key secondary estimands can be formulated similarly to the primary estimand described in Section 12.3.1, with the following modifications in regards to endpoint and population-level summary attributes. The binary 50% and 75% response variables across three 4-week intervals are calculated based on the available monthly values. Further details on the derivation of the endpoints can be found in Section 19.1.1.

50% response (Weeks 1-12)

- The **endpoint** to be obtained is a binary response variable indicating a successful response if a patient has achieved a 50% reduction or more in number of MMDs across weeks 1-12
- The **population-level summary** is the odds ratio of a successful response between eptinezumab and placebo

75% response (Weeks 1-12)

- The **endpoint** to be obtained is a binary response variable indicating a successful response if a patient has achieved a 75% reduction or more in number of MMDs across weeks 1-12
- The **population-level summary** is the odds ratio of a successful response between eptinezumab and placebo

Change from baseline in MMDs (Weeks 13-24)

- The **endpoint** to be obtained is the change from baseline in MMDs across weeks 13-24

- The **population-level summary** is the least squares mean difference between eptinezumab and placebo for the endpoint

Change from Baseline in HIT-6
For HIT-6, some of the intercurrent events will be addressed using different strategies than what is described for the primary and other key secondary estimands. Therefore, the phrasing of the key secondary estimand related to this endpoint is also a little different.

The differences to the strategies used for the primary and other key secondary estimands in the handling of intercurrent events are as follows:

- *Use of acute medication to treat a headache:* Instead of a hypothetical strategy, this intercurrent event will be handled using a treatment policy strategy, i.e. the values of HIT-6 are used regardless of whether the patient took any acute medication because they believed they were experiencing a migraine
- *Withdrawal due to lack of efficacy*: Will be addressed using a treatment policy strategy where the available values of HIT-6 are used regardless of patients withdrawing due to lack of efficacy
- *Withdrawal due to adverse event*: Will be addressed using a treatment policy strategy where the available values of HIT-6 are used regardless of patients withdrawing due to adverse events

Based on this, the key secondary estimand for evaluating the health-related quality of life and work productivity impact objective of the study will be the effect of eptinezumab on change from baseline in HIT-6 score regardless of patients withdrawing due to lack of efficacy or adverse events and regardless of use of acute or preventive migraine medication and infusion interruptions or terminations.

In addition, the following two attributes differ from the primary and other key secondary estimands:

- The **endpoint** to be obtained is the change from baseline in HIT-6 at Week 12
- The **population-level summary** is the least squares mean difference between eptinezumab and placebo for the endpoint

12.4.2 Analysis of the Key Secondary Endpoints

50% and 75% response
The two key secondary endpoints, 50% response (Weeks 1-12) and 75% response (Weeks 1-12) will be analysed using logistic regression. The model will include baseline MMDs as a continuous covariate, and treatment and stratification factor (MHDs at baseline: ≤14 />14) as factors. The SAS® code for these key secondary analyses is shown in Appendix IV.

The logistic regression model will be fitted using the maximum likelihood (ML) method and the logit link function.

The odds ratios for eptinezumab 300 mg and eptinezumab 100 mg compared to placebo will be estimated from the model and presented with p-values based on the likelihood ratio test and 95% CIs based on the profile likelihood.

The nominal p-values comparing each dose of eptinezumab to placebo will be presented. The comparisons will be part of the testing strategy described in Section 12.2.

In addition, the differences in response proportions between each dose of eptinezumab and placebo will be presented.

Change from Baseline in the number of MMDs (Weeks 13-24)
Changes from Baseline in MMDs at Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, and Weeks 21-24 will be analysed using the same methodology as described in Section 12.3.2 for the primary endpoint.

The mean differences between each dose of eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-visit interaction in the MMRM model. The estimates will be presented with nominal p-values and 95% CIs. The comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 13-24. The comparisons will be part of the testing strategy described in Section 12.2.

Change from Baseline in HIT-6
Changes from Baseline in HIT-6 total score at weeks 4, 8, 12, 16, 20, and 24 will be analysed using the same methodology as described in Section 12.3.2 for the primary endpoint, replacing baseline MMD score with baseline HIT-6 score in the model.

The mean differences between each dose of eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-visit interaction in the MMRM model. The estimates will be presented with nominal p-values and 95% CIs. The comparisons will be the contrasts between each dose of eptinezumab and placebo at Week 12. The comparisons will be part of the testing strategy described in Section 12.2.

12.4.3 Rationale for Selected Analysis Method for the Key Secondary Endpoints

The rationale for the selected analysis method for change from Baseline in the number of MMDs (Weeks 13-24) and change from Baseline in HIT-6 is covered by Section 12.3.4.

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

Although it is recognized that adjustment for predictive covariates will always, in contrast to classical linear regression models, result in a loss of precision (or no change) of the estimates, the adjustment for predictive covariates will result in greater efficiency/higher power when testing for a treatment effect in a randomized study.[2,3] The chosen covariate is considered to

be highly predictive for the response, and thus the logistic regression model is considered valid as a key secondary analysis model.

12.4.4 Sensitivity Analyses of the Key Secondary Endpoints

For the two key secondary endpoints, 50% response (Weeks 1-12) and 75% response (Weeks 1-12), a sensitivity analysis will be performed, where any patient that does not have a value of MMDs for all 3 post-baseline 4-week periods included in Weeks 1-12 will be imputed with a non-response.

For the key secondary endpoint, change from baseline in the number of MMDs (Weeks 13-24), a sensitivity analysis will be conducted similarly to the one described for the primary endpoint under *Imputation for Weeks 1-4* (Section 12.3.5), i.e. where monthly values in the first 4 weeks after first infusion are calculated using the *weighting* rule described in Section 19.1.1.1 if patients have less than 14 days with eDiary reporting in this period.

For the key secondary endpoint, change from baseline in HIT-6 total score, a sensitivity analysis using the placebo-based multiple imputation method to assess the robustness of the conclusions for this endpoint to the type of missing data will be conducted.

An analysis will be performed using a pattern-mixture model (PMM), in which missing HIT-6 total scores will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the placebo group.[4]

200 simulations will be performed to generate the datasets that will be analysed using the model described in section 12.4.2.These analyses will be combined using Rubin's rule to form a unique point estimate and standard error, taking into account the uncertainty of the imputation.[5] The SAS® code for this sensitivity analysis is shown in Appendix IV.

12.5 Analysis of the Secondary Endpoints

The following endpoints will be derived according to the descriptions given in Section 19.1 and analysed using the same methodology as that described for the primary endpoint (see Section 12.3.2) with a few exceptions, which are highlighted below the list:

- Change from baseline in the number of MHDs (Weeks 1-12)
- Change from baseline in percentage of migraine/headaches with severe pain intensity (Weeks 1- 12)
- Change from baseline in the number of MMDs with use of acute medication (Weeks 1- 12 and Weeks 13-24)
- Change from baseline in the number of monthly days with use of acute migraine medication (Weeks 1-12 and Weeks 13-24)
- PGIC score at Week 12 and at Week 24
- Change from baseline in the number of MMDs in patients with MOH (Weeks 1-12)
- MBS score at Week 12
- Change from baseline to Week 24 in the HIT-6 score

- Change from baseline to Week 12 and to Week 24 in MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function)
- Change from baseline to Week 12 and to Week 24 in EQ-5D-5L VAS score
- Change from baseline to Week 12 and to Week 24 in WPAI sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment)

For the endpoints listed above, the baseline MMD score will be replaced with the baseline score for the endpoint in question in the model except for analysis of PGIC and MBS, which will exclude the baseline score terms, since the rating of the scales in themselves represent a change from baseline so no baseline score exists.

In the analysis of MHDs, the model will include following fixed effects: month, country, and treatment as factors, baseline MHDs as a continuous covariate, treatment-by-month interaction, and baseline score-by-month interaction.

The analysis of MMDs in patients with MOH will only be performed if the number of patients with MOH constitutes a sufficiently large part of the study population.

For HIT-6, in addition to summary tables presenting descriptive statistics for the total score, tables presenting the counts and percentages of patient in each life impact category as defined in Section 19.1.4 will be produced by visit and treatment group.

The following endpoints will be analysed using the same methodology as that described for the key secondary response endpoints (see Section 12.4.2):

- Response: Patients with 50% reduction from baseline in MMDs (Weeks 13-24)
- Response: Patients with 75% reduction from baseline in MMDs (Weeks 13-24)
- Response: Patients with 50% reduction from baseline in MHDs (Weeks 1-12)
- Response: Patients with 75% reduction from baseline in MHDs (Weeks 1-12)
- Response: Patients with a 5-point reduction from baseline to Week 12 and from baseline to Week 24 in HIT-6

For the HIT-6 response endpoints, LOCF will be used to impute a potentially missing value at Week 12 or Week 24. Baseline values will not be carried forward.

The following endpoints:

- Response: Patients with 100% reduction from baseline in MMDs (Weeks 1-12)
- Response: Patients with 100% reduction from baseline in MHDs (Weeks 1-12)
- Patients with a migraine on the day after first dosing

Will be derived according to the descriptions in Section 19.1.1.2 and 19.1.1.3 and analysed using an extended Cochran-Mantel-Haenszel (CMH) test, adjusting for one of the stratification factors (MHDs at baseline: ≤14 />14). The rates for each dose of eptinezumab and placebo will be presented. The SAS® code for performing the extended CMH test is shown in Appendix IV.

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

Tables displaying the counts and percentage of answers to each category of response options for each item of EQ-5D-5L will be presented by visit and treatment group. Furthermore, shift tables displaying for each item in EQ-5D-5L the number and percentage of patients who decreased, increased or had no change from baseline in the item score will be provided by visit and treatment group.

For inclusion into the *addendum CSR,* the endpoints listed below will be derived according to the descriptions given in Section 19.1 and the absolute values will be analysed using an MMRM similar to the one described for the primary endpoint (see Section 12.3.2) but using treatment sequence group instead of treatment group.

No treatment comparisons will be performed for any of the efficacy endpoints after Week 24. Instead, the estimated mean values will be reported with two-sided 95% confidence intervals by treatment sequence for:

- Number of MMDs (at Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24, Weeks 25-36, 37-48, 49-60, and 61-72)
- HIT-6 score (at week 4, 8, 12, 16, 20, 24, 36, 48, 60, and 72)

The absolute values and changes from baseline in MMDs at Weeks 25-36, 37-48, 49-60, and 61-72 will be summarized descriptively by treatment sequence group and by treatment group in the Extension Period.

Similarly, the absolute values and changes from baseline in HIT-6 total score at Weeks 36, 48, 60, and 72 will be summarized descriptively by treatment sequence group and by treatment group in the Extension Period.

Tables displaying the counts and proportion of patients achieving a 50% and 75% reduction from baseline in MMDs across Weeks 25-36, 37-48, 49-60, and 61-72 will be presented by treatment sequence group and by treatment group in the Extension Period.

12.6 Analysis of the Exploratory Endpoints

The exploratory endpoints change from baseline in number of monthly headache episodes and migraine attacks for Weeks 1-12 and Weeks 13-24 will be evaluated similarly to the primary endpoint (see Section 12.3.2).

All the exploratory endpoints related to the eDiary or scales endpoints after Week 24 will be analysed similarly to what is described in Section 12.5, for inclusion into the *addendum CSR*.

13 Safety

13.1 Adverse Events

13.1.1 General Methodology for Adverse Events

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

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

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order based on the percentages of patients with these adverse events in the eptinezumab 300 mg dose group.

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

Listings of adverse events will be sorted by site, treatment group, patient 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, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included. In listings of adverse events, start or stop dates will be displayed as collected also in case of partially or completely missing dates.

13.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 23.0 or later.

13.1.3 Classification of Adverse Events

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

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date and time of first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity 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 19.3.5. Note that adverse events with incomplete start dates will be classified as treatment-emergent simply if the imputed start date is on or after the date of first IMP infusion, since the start time of the adverse event will not be imputed, unless the investigator in such a case has assessed that the causality to IMP is "Not Related - Prior to IMP".

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

13.1.4 Allocation of TEAEs to Treatment Periods

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

- *TEAE in the Placebo-controlled Period* – a TEAE that starts before the date and time of the start of Visit 8 IMP infusion
- *TEAE in the Extension Period* – a TEAE that starts during or after administration of Visit 8 IMP infusion

For allocation of TEAEs to treatment periods, the same rule for imputed dates as specified above (in Section 13.1.3) applies, i.e. for incomplete start dates, only the imputed start date and not the time (which will not be imputed) of the adverse event will be taken into account in the allocation of the TEAE to periods.

If an adverse event starts on the day of the Visit 8 IMP infusion but with an unknown start time, the adverse event will be classified as treatment-emergent in the Placebo-controlled period.

13.1.5 Presentation of Adverse Events

A listing of all adverse events starting at or after entering the Extension Period, including a flag for TEAEs will be included in the *addendum to CSR* based on the APTS_LT.

A similar listing of all adverse events occurring before entering the Extension Period will be produced for the *CSR* based on APRS.

For each period, an overview of the numbers and percentages of patients with TEAEs, serious adverse events (SAEs), TEAEs leading to infusion interruption, TEAEs leading to withdrawal, and of patients who died will be provided based on the APTS/APTS_LT. For TEAEs, SAEs, and TEAEs leading to withdrawal, the total number of events will be included.

13.1.6 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided for the Placebo-controlled Period and for the Extension Period:

- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs by sex and preferred term
- TEAEs with an incidence ≥2% in any treatment group by preferred term
- causally related TEAEs by SOC and preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*), SOC, and preferred term

- causally related TEAEs by intensity, SOC, and preferred term
- TEAEs occurring on the day of dosing after infusion start by SOC and preferred term (this includes day of V2 and V5 infusion for the Placebo-controlled Period and day of V8, V11, V14, and V17 infusion for the Extension Period)

The summaries will be provided for the APTS for the Placebo-controlled Period and for APTS_LT for the Extension Period.

For the Extension Period, the two tables summarizing all TEAEs by SOC and preferred term and all TEAEs by preferred term will include two additional columns displaying the totals for eptinezumab 100 mg and eptinezumab 300 mg.

For TEAEs occurring on the day of dosing after infusion start, TEAEs with missing start times will also be included.

13.1.7 Presentation of Deaths

All the adverse events in patients who died before entering the Extension Period will be listed for the APRS for inclusion in the *CSR*.

All the adverse events in patients who died after entering the Extension Period will be listed for the APTS_LT for inclusion in the *addendum to CSR*.

13.1.8 Presentation of Serious Adverse Events

All SAEs occurring before entering the Extension Period will be listed for the APRS for inclusion in the *CSR*.

All SAEs occurring at or after entering the Extension Period will be listed for the APTS_LT for inclusion in the *addendum to CSR*.

Treatment-emergent SAEs will be summarized for the Placebo-controlled Period based on APTS and for the Extension Period based on APTS_LT by:

- SOC and preferred term
- preferred term

13.1.9 Presentation of Adverse Events Leading to Withdrawal

All AEs leading to withdrawal before entering the Extension Period will be listed for the APRS for inclusion in the *CSR*.

All AEs leading to withdrawal occurring at or after entering the Extension Period will be listed for the APTS_LT for inclusion in the *addendum to CSR*.

TEAEs leading to withdrawal will be summarized for the Placebo-controlled Period based on APTS and for the Extension Period based on APTS_LT by:

- SOC and preferred term
- preferred term

13.1.10 Presentation of Adverse Events Leading to Study Drug Infusion Interruption

All AEs leading to study drug infusion interruption before entering the Extension Period will be listed for the APRS for inclusion in the *CSR*.

All AEs leading to study drug infusion interruption occurring at or after entering the Extension Period will be listed for the APTS_LT for inclusion in the *addendum to CSR*.

TEAEs leading to study drug infusion interruption will be summarized for the Placebo-controlled Period based on APTS and for the Extension Period based on APTS_LT by:

- SOC and preferred term
- preferred term

13.1.11 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 6.

All AESIs occurring before entering the Extension Period will be listed for the APRS for inclusion in the *CSR*.

All AESIs occurring at or after entering the Extension Period will be listed for the APTS_LT for inclusion in the *addendum to CSR*.

The listings will be repeated for all AEs belonging to the Hypersensitivity and Anaphylactic Reactions event category only, see Table 6.

The following summaries of treatment-emergent AESIs will be provided for the Placebo-controlled Period and for the Extension Period:

- 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 for the Placebo-controlled Period and for APTS_LT for the Extension Period.

13.2 General Methodology for Other Safety Data

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

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

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

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

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

For patients with post-baseline PCS values in the Placebo-controlled Period, listings will be provided including all the values for those patients for the variable prior to entering the Extension Period, with flagging of PCS values and out-of-reference-range values for inclusion in the *CSR*.

For patients with PCS values occurring after start of V8 IMP infusion, similar listings will be provided including all the values for those patients for the variable for inclusion in the *addendum to CSR*.

For inclusion in the *CSR*, all the adverse events occurring before entering the Extension Period in patients with post-baseline PCS values in the Placebo-controlled Period will be listed by treatment group and patient 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.

Similar listings will be provided for patients with PCS values occurring after start of V8 IMP infusion, including all the adverse events for the patients, for inclusion in the *addendum to CSR*.

For urine dipsticks, for which the results are categorical values (for example, negative, trace, 1+, 2+), the number and percentage of patients will be summarized by visit for each test, separately for each period. The microscopy results will be listed by assessment time point for patients with findings.

13.3 Clinical Safety Laboratory Test Data

13.3.1 Data Presentation

The PCS criteria used for the clinical safety laboratory tests can be found in Table 3.

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

13.3.2 Anti-Drug Antibody (ADA) including Neutralizing Antibody (NAb) assessments

Analysis of specific anti-eptinezumab antibodies is restricted to subjects who are randomized to eptinezumab.

For subjects with pre-existing antibodies at Baseline, the number and percent of subjects who are positive for anti-eptinezumab antibody will be summarized. In addition, the number and percent of subjects who develop anti-drug antibodies to eptinezumab during the trial will be summarized at each scheduled visit. Denominators for percentages will be the total number of samples taken for the specified visit. For patients with ADA, neutralizing properties of anti-eptinezumab antibodies will also be summarized.

All the immunogenicity data will be listed by period.

Subjects with a positive anti-eptinezumab antibody result will be listed by period.

For inclusion in the CSR, all the adverse events occurring before entering the Extension Period in patients with positive anti-eptinezumab antibody results in the Placebo-controlled Period or with pre-existing antibodies at Baseline, will be listed. The listing will include the ADA result, the assessment date, the preferred term for the adverse event, and start date and stop date of the adverse event. The ADA results and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

Similar listings will be provided for patients with ADA-positive results occurring after start of V8 IMP infusion, including all the adverse events for the patients, for inclusion in the addendum to CSR.

In addition, summaries of TEAEs by SOC and preferred term will be provided for the Placebo-controlled Period and for the Extension Period for patients who are ADA-positive.

13.3.3 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[6] using the following criteria:

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

Patients fulfilling any of the criteria in the Placebo-controlled Period will be listed for inclusion in the *CSR*, and the listing will include all the ALT, AST, BILI, and ALP values for those patients prior to entering the Extension Period, 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).

A similar listing will be provided including all the ALT, AST, BILI and ALP values for the patients fulfilling any of the criteria in the Extension Period for inclusion in the *addendum to CSR*.

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

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

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

13.4 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 4.

13.5 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 5.

In addition to the tables and listings specified in Section 13.2, absolute values and changes from Baseline in QTcF will also be summarized categorically by visit and treatment, separately for the Placebo-controlled Period and the Extension Period. The categories that will be used are as follows for the absolute QTcF values:

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

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

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

Furthermore, the number and percentage of patients being classified as having either a normal, abnormal but not clinically significant, abnormal and clinically significant ECG result

based on the overall interpretation of the ECG from the investigator will be summarized by visit and treatment group, separately for each period.

13.6 Other Safety Endpoints

13.6.1 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 12 months at screening (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening that focuses on the last 12 months
- at baseline (using the *Since Last Visit Version*) – the C-SSRS assessment at baseline that collects information since the previous visit
- post-baseline (using the *Since Last Visit Version*) – the C-SSRS assessments after baseline

The numbers and percentages of patients with lifetime, past 12 months, baseline, or post-baseline suicide-related events based on the C-SSRS will be summarized by treatment group. For each summary, the most severe item with an answer "Yes" for each patient according to the ordering given in Panel 4 is displayed. For the post-baseline assessments, the summaries will be by treatment group and period and the most severe item with an answer "Yes" for the whole period for each patient related to suicidal ideation and/or behaviour will be summarized.

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

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 the lifetime, past 12 months, baseline and Placebo-controlled Period summaries and based on the APTS_LT for the

Extension Period summary. Patients with at least one C-SSRS assessment in the period will be included, 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 patients with any post-baseline suicidal ideation or behaviour in the Placebo-controlled Period (C-SSRS scores of 1 to 10), listings will be provided based on APRS including all C-SSRS scores prior to entering the Extension Period for those patients for inclusion in the *CSR*.

A similar listing will be provided for patients with any post-baseline suicidal ideation or behaviour in the Extension Period including all the C-SSRS scores for those patients for inclusion in the *addendum to CSR*.

14 Blinded Data Reviews

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

An independent Safety Data Monitoring Committee (DMC) will regularly monitor the patients' safety data according to the *DMC Charter*. The DMC will have access to unblinded information for the double-blind treatment for each patient. Members of the DMC will not be involved in other study-related tasks.

15 Interim Analyses

See Section 18.

16 Sample Size Considerations

The two prior eptinezumab Phase III studies, PROMISE-1 performed in an EM population and PROMISE-2 performed in a CM population, had the following effect sizes for the primary endpoint when compared to placebo (standard deviations):

- EM: 100 mg 0.69 (3.1), 300 mg 1.11 (3.1)
- CM: 100 mg 2.03 (5.8), 300 mg 2.60 (5.8)

The power was determined by simulating the testing strategy (10000 simulations) assuming normal distributions with similar mean and SD for continuous endpoints and similar success rates as the response variables in the Phase III studies for the corresponding population (EM or CM) without assuming the variables to be correlated. With 280 patients per treatment group, assuming that 40% of the patients will be from the EM population and 60% from the

CM population, and that 2% of the patients not having a post-baseline assessment of the primary endpoint, simulations show that the power for the test of the primary endpoint is approximately 94% for the comparison of 100 mg to placebo and 99% power for the comparison of 300 mg to placebo. The individual key secondary endpoints had a power of at least 68% for showing an effect, with a combined power of 58% for seeing an effect for all primary and key secondary endpoints and both doses in the testing strategy.

17 Statistical Software

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

18 Changes to Analyses Specified in the Protocol

In the *Clinical Study Protocol* (ed. 1.0 and 2.0), it is described that an unblinded interim analysis for efficacy will be performed, when 345 patients have been randomized and received the first infusion of IMP and have had the opportunity to complete the Primary Outcome Visit (Week 12). The analysis was intended to allow for stopping the study for efficacy if the results fulfilled the interim criteria. Based on the result of the interim analysis, Lundbeck could decide to stop the study for efficacy or continue the enrolment. Due to recruitment being faster than expected, it has been decided not to conduct the interim analysis after all. Therefore, any references to the interim analysis have been removed from the *Statistical Analysis Plan*, and the significance level to be used in the testing strategy has been updated to 0.05.

The wording of endpoints related to HCRU has been updated since it is not the changes from baseline but the frequency of responses in each category that will be summarized for the study.

The wording of endpoints related to MBS has been updated to reflect that the MBS score in itself reflects a change from baseline.

HIT-6 responder endpoints have been added to the list of secondary endpoints.

In relation to the addition of HIT-6 response endpoints, responder analyses using logistic regression have been added to the list of secondary analyses.

According to the original *Clinical Study Protocol* ed. 1.0, the primary analysis of the primary endpoint has been updated from an ANCOVA using the average values of MMDs over Weeks 1-12 to an MMRM using the available monthly values of MMDs. This update is included in an amendment of the *Clinical Study Protocol*, resulting in a *Clinical Study Protocol* ed. 2.0, dated 22 January 2021.

According to the original *Clinical Study Protocol* ed. 1.0, the key secondary analyses of key secondary responder endpoints (50% response (Weeks 1-12) and 75% response (Weeks 1-12)) have been updated to logistic regressions instead of the CMH tests specified in the

protocol. This update is included in an amendment of the *Clinical Study Protocol*, resulting in a *Clinical Study Protocol* ed. 2.0, dated 22 January 2021.

The definition of a *treatment-emergent adverse event* (TEAE) has been updated to clarify that the time of infusion is also taken into account in the classification.

For the numerical representation of PGIC scores, the score 1 is used to represent a score of "very much improved" and a score of 7 to represent a score of "very much worse". This is the opposite of what is described in the protocol, where it is stated that a high score indicates improvement.

19 Details on Data Handling

19.1 Derived Variables

19.1.1 eDiary

19.1.1.1 Monthly Migraine Days (MMDs)/Monthly Headache Days (MHDs)

The following describes the derivation of MMDs. The derivation of MHDs follows the same principles.

4-Week Intervals

For Baseline and each 4-week period post-baseline in the study, the number of MMDs will be derived as the number of migraine days within each 28-day interval using the imputation rules described below. The 4-week periods post-baseline that are considered are the following: Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, Weeks 21-24, Weeks 25-28, Weeks 29-32, Weeks 33-36, Weeks 37-40, Weeks 41-44, Weeks 45-48, Weeks 49-52, Weeks 53-56, Weeks 57-60, Weeks 61-64, Weeks 65-68, Weeks 69-72.

In general, for 4-week periods where the eDiary is completed on at least 14 days out of the 28 days, prorating will be used to calculate the MMDs, and for 4-week periods where the eDiary is completed on less than 14 days out of the 28 days, the MMDs will be set to missing. However, there are cases where weighting will be used when less than 14 days have been completed, and an overview is given in Panel 5.

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

28(Reported Migraine Days/Reported eDiary Days)*

This imputation rule will also be used for the Baseline value regardless of the number of reported eDiary days in the screening period. Patients are, however, required to demonstrate compliance with the eDiary and fill it out for at least 24 out of the 28 days in the screening period in order to be eligible for randomization.

Weighting
Intended to be used in special cases for the first 4-week period post-baseline, where the eDiary is completed on less than 14 days out of the 28 days due to withdrawal. When weighting is used, the number of MMDs is derived as a weighted sum of the observed mean number of migraine days in the period and the mean MMDs for the preceding period as follows:

$$28*(W*X + (1 - W)*X_p),$$

where W = *Reported eDiary Days/13,* X = *Reported Migraine Days/Reported eDiary Days,* and X_p = *preceding MMDs/28*.

Patients who withdraw due to lack of efficacy so early that they only have post-baseline data from Weeks 1-4 will have their MMDs calculated using weighting for Weeks 1-4 if they have less than 14 days of eDiary reporting during the first 4 weeks of the study. If they have 14 days or more in this period, their MMDs for Weeks 1-4 will be calculated using prorating.

Patients who withdraw due to adverse events so early that they only have post-baseline data from Weeks 1-4 will have their MMDs calculated using weighting for Weeks 1-4 if they have less than 14 days of eDiary reporting during the first 4 weeks of the study. If they have 14 days or more in this period, their MMDs for Weeks 1-4 will be calculated using prorating.

Panel 5 Overview of Imputation Rules for 4-Week Periods for eDiary Data

		Number of Reported eDiary Days in Period	
Description	**4-Week Period**	**0-13**	**14-28**
All patients randomized	Baseline	Prorating*	Prorating
Patients not withdrawing due to lack of efficacy/adverse event	Weeks 1-4	None (missing)	Prorating
Patients not withdrawing due to lack of efficacy/adverse event	4-week periods after week 4	None (missing)	Prorating
Patients withdrawing due to lack of efficacy	Weeks 1- 4	Weighting	Prorating
Patients withdrawing due to lack of efficacy	4-week periods after week 4	None (missing)	Prorating
Patients withdrawing due to adverse event	Weeks 1-4	Weighting	Prorating
Patients withdrawing due to adverse event	4-week periods after week 4	None (missing)	Prorating

*Patients are required to complete the eDiary for at least 24 days during the first 28 days of screening to be eligible

In case of a reporting day where a patient answers in the evening diary that they experienced a headache on that day but then never fills out an actual headache in the headache diary, the day will be assigned as a no headache and no migraine day.

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

19.1.1.2 Migraine/Headache Responder Rates

The following describes the derivation for monthly migraine days. The derivation for monthly headache days is similar.

The following responder rates will be derived: 50%, 75%, and 100%. A responder is a patient, who achieves a ≥50% reduction, ≥75% reduction, or 100% reduction in MMDs, respectively, compared to the baseline number of MMDs. The derivation of these responder endpoints will be based on the number of MMDs resulting from the imputations described in Section 19.1.1.1.

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

For the 12-week and 24-week intervals, the 50% and 75% responder status will be derived as follows, using 50% response for Weeks 1-12 as an example:

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

where Δ_{Mi} is the change from baseline value for month *i*. For 12-week intervals, if any of the months included in the calculation have a missing value of MMDs, the responder status will be derived based on the available values. For 24-week intervals, the responder status will only be calculated if at least one observation from each 12-week period is available, i.e. it will be non-missing if there is one observation from one of Weeks 1-4, Weeks 5-8, or Weeks 9-12 and one of Weeks 13-16, Weeks 17-20, or Weeks 21-24.

The 100% responder rate for the 12-week and 24-week intervals will be derived based on the average 100% responder status for the 4-week intervals included in the interval, i.e. if a patient has 100% response for Weeks 1-4 and Weeks 5-8 but not for Weeks 9-12, the 100% responder rate will be 0.67 (computed as (1 + 1 + 0)/3), since the responder status for the first and second month for the patient was 1 and the responder status for the third month was 0. If any of the months included have a missing value of MMDs, the patient will be imputed with a non-response, i.e. with the value 0, for the 12-week or 24-week interval.

19.1.1.3 Percentage of Patients with Migraines

Day 1

The percentage of patients with a migraine on the day after first dosing will be derived based on whether the patient filled out the eDiary on Day 1 or not. If the patient filled out the eDiary on Day 1, the patient will have a rate of either 0 or 100 on Day 1 that is, 0 if the patient experienced no migraine on Day 1 and 100 if the patient did experience a migraine on Day 1.

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

$$100*(\textit{Number of MMDs Weeks 1-4}/28),$$

where the number of MMDs for Weeks 1-4 is derived as described in Section 19.1.1.1. Note that if the number of MMDs for Weeks 1-4 is missing for the patient and the patient did not fill out the eDiary on Day 1, the Day 1 rate will be missing.

Similarly, the rate for having a migraine on Day 1 after the Week 12 dosing will be imputed using the MMDs for Weeks 13-16 in case of a missing eDiary report on that day.

19.1.1.4 Migraines/Headaches With Severe Pain Intensity and Headache Episodes/Migraine Attacks

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

A migraine attack is defined as 1 continuously recorded migraine. One attack may result in multiple migraine days. Headache episodes are similarly defined. Headache severity is collected on a 3-point scale, Mild, Moderate and Severe. Migraines and headaches with severe pain intensity are defined as migraine attacks/headache episodes with a reported severity of "Severe".

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

The derivation of the number of monthly migraine attacks will follow the imputation rules described in Section 19.1.1.1 for MMDs, replacing *Reported Migraine Days* with *Reported Migraine Attacks* everywhere. As an example, the number of monthly migraine attacks for a patient with 14 days or more of eDiary reporting in a 4-week period will be derived as:

$$28*(\textit{Reported Migraine Attacks}/\textit{Reported eDiary Days})$$

And for a patient who withdraws due to an adverse event or lack of efficacy within the first 28 days post baseline with less than 14 days of eDiary reporting in the first 4-week period, the number of monthly migraine attacks will be derived as:

$$28*(W*X^{att} + (1 - W)*X_p^{att}),$$

where *W = Reported eDiary Days/13, X^{att} = Reported Migraine Attacks/Reported eDiary Days,* and *X_p^{att} = preceding Number of Migraine Attacks/28*.

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

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

The average length of headache episodes and migraine attacks will also be derived and will be based on the number of monthly migraine attacks and headache episodes. The number of monthly hours with headache and migraine will be derived similarly to how the number of monthly migraine attacks and headache episodes are derived, i.e. to derive the monthly number of migraine hours, *Reported Migraine Attacks* is replaced with *Reported Migraine Hours* in the calculations described above. From that, the average length of headache episodes and migraine attacks is calculated as the monthly hours with headache or migraine divided by the number of monthly headache episodes or migraine attacks, respectively. Patients with no migraine attacks/headache episodes are included with an average length of 0 for the month.

19.1.1.5 Monthly Days with Acute Migraine Medication Usage and MMDs/MHDs with Acute Medication Usage

In the evening eDiary, patients are asked each day to fill out whether they used any of the following medications during that day: Ergotamine, triptan, analgesic, opioid, or combination analgesic. A day where the patient answers that they took any of those in the evening eDiary is considered a day with use of acute migraine medication.

The number of days with acute migraine medication usage is then derived for each 4-week period using the imputations described in Section 19.1.1.1 and replacing *Reported Migraine Days* with *Reported Acute Migraine Medication Days* everywhere as well as replacing *Reported eDiary Days* with *Reported Evening eDiary Days*, where a "*Reported Evening eDiary Day*" is defined as any day where the evening eDiary has been filled out.

Similarly, the number of days with each of the medication types taken will be derived as well as the number of days with ergotamine and triptan use.

Additionally, the monthly migraine days/monthly headache days with acute medication usage will be derived. This is derived using the answer to "*Did you take any medications to treat this headache?"* in the headache diary. The question is asked when a patient is ending a headache. Thus, a migraine/headache day with acute medication usage is defined as a migraine/headache day with the extra condition that this question has been answered as "Yes". In case of a migraine/headache with acute medication usage spanning multiple days, all the days will be counted as a migraine/headache day with use of acute medication.

19.1.2 Patient Global Impression of Change (PGIC)

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

The item is rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

19.1.3 Most Bothersome Symptom (MBS)

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

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

19.1.4 Headache Impact Test (HIT-6)

The HIT-6 (v1.0)[7] is a Likert-type, self-reporting questionnaire designed to assess the impact of an occurring headache and its effect on the ability to function normally in daily life. The HIT-6 contains 6 questions, each item is rated from "never" to "always" with the following response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. The total score for the HIT-6 is the sum of each response score and ranges from 36 to 78. The life impact derived from the total score is described as followed: Severe (≥60), Substantial (56-59), Some (50-55), Little to None (≤49).

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

The MSQ v2.1[8] is a patient-reported outcome designed to assess the quality of life in patients with migraine. It consists of 14 items covering three domains: role function restrictive (7 items); role function preventive (4 items); and emotional function (3 items). Each item is scored on a 6-point scale ranging from 1 (none of the time) to 6 (all of the time).

The items going into each domain[9] are specified in Panel 6.

Each item score is mapped from the recorded value of the item as shown in Panel 7.[10]

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

Panel 6 MSQ v.2.1 Domains

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

Panel 7 MSQ v.2.1 Item Values

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

Panel 8 Derivation of MSQ v.2.1 Domain Scores

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

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

The EQ-5D-5L[11] is a patient-reported assessment designed to measure the patient's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated.

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

19.1.7 Health Care Resource Utilization (HCRU)

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

The items from the questionnaire will be analyzed separately.

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

The WPAI[12] is a patient self-rated scale designed to provide a quantitative measure of the work productivity and activity impairment due to a specific health problem (WPAI:M). The WPAI assesses activities over the preceding 7 days and consists of 6 items: 3 items assess the number of hours worked, the number of hours missed from work due to the patient's condition, or due to other reasons, and 2 visual numerical scales to assess how much the patient's condition affects their productivity at work and their ability to complete normal daily activities.

The derivation of the WPAI:M sub-scores[13] is given in Panel 9, where Q1-Q6 refers to question 1-6 in the questionnaire. If both Q2 and Q4 has a score of 0 then both the Absenteeism and the Work productivity loss sub-scores are set to missing.

Panel 9 Derivation of WPAI:M sub-scores

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

19.2 Assigning Data to Visits

See Section 4.2 for definition of Baseline values.

19.2.1 Clinical Outcome Assessments (COAs) - Scales

For treated patients withdrawing prior to Week 24, the withdrawal visit scheduled 12 weeks after the last IMP infusion will also include efficacy evaluations (PGIC, MBS, HIT-6, MSQ, EQ-5D-5L, HCRU, and WPAI:M). These assessments will be assigned to either Visit 5 or Visit 8 according to when the patient was withdrawn as follows:

- For patients withdrawing prior to Visit 5, the assessments from the Withdrawal Visit will be assigned to nominal Visit 5
- For patients withdrawing after Visit 5 (but prior to Visit 8), the assessments from the Withdrawal Visit will be assigned to nominal Visit 8.

Unscheduled visits will not contain assessments of the COAs mentioned above. In relation to the nominal visits post-Baseline, a patient 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 patient fills out the scales 3 days before the visit and the visit is postponed afterwards implying that the patient has to complete the COA again, the latest assessment will be used.

19.2.2 Safety Variables

Laboratory Tests and ECG

Assessments of laboratory tests and ECGs at unscheduled visits and withdrawal visits will be assigned to a nominal visit in the Placebo-controlled Period according to the visit windowing specified in Panel 10 for patients in the APTS. Assessments for patients not receiving any infusions of IMP will be assigned to Visit 2 (Baseline). For patients receiving an infusion of

IMP in the Extension Period, assessments of laboratory tests and ECGs at unscheduled visits and withdrawal visits will be assigned to a nominal visit in the Extension Period according to the visit windowing specified in Panel 11.

Panel 10 Visit Windows for Placebo-Controlled Period – Laboratory tests, ECG

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Screening Visit)	-4	-28	NA
V2 (Baseline Visit)	0	0	NA
V5	12	84	After start of first IMP infusion to day 126
V8	24	168	Day 127 to start of Visit 8 IMP infusion

Panel 11 Visit Windows for Extension Period – Laboratory tests, ECG

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Nominal Visit Day Relative to Visit 8 IMP Infusion	Time Window Relative to Visit 8 IMP Infusion
V11	36	252	84	After start of Visit 8 IMP infusion to day 126
V14	48	336	168	Day 127 to day 210
V17	60	420	252	Day 211 to day 294
V20	72	504	336	> 294

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 Panel 13.

Panel 12 Visit Windows for Placebo-Controlled Period – Vital Signs

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Screening Visit)	-4	-28	NA
V2 (Baseline Visit) pre-dose	0	0	NA
V2 (Baseline Visit) post-dose	0	0	After start of first IMP infusion to day 42
V5 pre-dose	12	84	Day 43 to start of V5 IMP infusion
V5 post-dose	12	84	After start of V5 IMP infusion to day 126
V8 pre-dose	24	168	Day 127 to start of Visit 8 IMP infusion

Panel 13 Visit Windows for Extension Period – Vital Signs

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Nominal Visit Day Relative to Visit 8 IMP Infusion	Time Window Relative to Visit 8 IMP Infusion
V8 post-dose	24	168	0	After start of V8 IMP infusion to day 42
V11 pre-dose	36	252	84	Day 43 to start of V11 IMP infusion
V11 post-dose	36	252	84	After start of V11 IMP infusion to day 126
V14 pre-dose	48	336	168	Day 127 to start of V14 IMP infusion
V14 post-dose	48	336	168	After start of V14 IMP infusion to day 210
V17 pre-dose	60	420	252	Day 211 to start of V17 IMP infusion
V17 post-dose	60	420	252	After start of V17 IMP infusion to day 294
V20	72	504	336	> 294

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.

19.3 Handling Missing or Incomplete Dates/Times

19.3.1 Missing Headache End Date and Time

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

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

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

Headaches that are not reported as stopped by the patient are missing the answers to the questions that allow for the determination of whether the headache was a migraine or not. Headaches with missing 'end' information will be classified as migraines (and thereby also as headaches).

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

19.3.2 Withdrawal Date

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

19.3.3 Medical Disorder Start and Stop Dates

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

19.3.4 Medication Start and Stop Dates

Imputation of incomplete or partially missing dates will be performed in order to document the assigned categories specified in Section 9.

The algorithm for imputing the start dates will follow the one used for imputing adverse event start dates, see Section 19.3.5.

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

- UK-MMM-YYYY: Medication end date is imputed with the last day of the month
- UK-UKN-YYYY: Medication end date is imputed with 31-DEC-YYYY

Medications marked as ongoing are considered concomitant medications in one or both of the periods (Placebo-controlled Period and Extension Period), depending on the (possibly imputed) start date, i.e. if the start date is at or after the date of V8 IMP infusion, the medication is only considered ongoing in the Extension Period.

19.3.5 Adverse Event Start and Stop Dates

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

Patients with no IMP infusion

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

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

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

Patients who received at least one IMP infusion

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

- UK-MMM-YYYY:
  - If the year and month are equal to the year and month of treatment start date, the adverse event start date is imputed with the date of first dose of IMP
  - If the year is equal to the year of treatment start date: If the month is prior to the treatment start date, the adverse event start date is imputed with the last day of the month. If the month is equal to the month of the treatment start date, see above. If the month is after the month of the treatment start date, the adverse event start date is imputed with the first day of the month

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

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

End Dates

Missing AE end dates will not be imputed.

Incomplete Intensity Change Dates

If the day is missing in a date of intensity change for an adverse event, the date will be imputed using the same algorithm as described above for incomplete adverse event start dates.

If this results in an imputed start date that is after the end date of the original event or after an intensity change that comes after the intensity change in question, the start date will be imputed with the end date of the original event or the date of the later intensity or change.

19.4 Data with Multiple Records

19.4.1 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 Section 9), each dose is considered a separate medication, and the same medication can be assigned to several categories for the same patient. Within a category, multiple entries contribute as a single count.

19.4.2 Changes in Intensity or Seriousness of Adverse Events

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

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

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

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

References

1. International Headache Society (IHS), Headache Classification Committee. The International Classification of Headache Disorders, 3rd edition 2018 (ICHD-3 2018).
2. Robinson LD and Jewell NP. Some surprising results about covariate adjustment in logistic regression models. International Statistical Review. 1991; 59: 227-240.
3. Koch GG, Tangen CM, Jung J-W, Amara IA. Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. Statist Med. 1998; 17: 1863-1892.
4. Little R and Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics. 1996; 52: 1324-1333.
5. Rubin, DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1997.
6. United States Food and Drug Administration (US FDA). Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009.
7. Kosinski M, Bayliss MS, Bjorner JB, Ware JE, Garber WH, Cady R, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res. 2003; 12(8): 963–974.
8. Jhingran P, Osterhaus JT, Miller DW, Lee JT, Kirchdoerfer L. Development and validation of the Migraine-Specific Quality of Life Questionnaire. Headache. 1998; 38(4): 295–302.
9. Martin BC, Pathak DS, Sharfman MI, Adelman JU, Taylor F, Kwong WJ, Jhingran P. Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). Headache. 2000 Mar; 40(3): 204-215.
10. Mapi Research Trust. Migraine specific quality of life questionnaire. Version 2.1. Scaling and scoring. Version 1.0. November 2017.
11. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011; 20: 1727–1736.
12. Reilly MC, Zbrozek AS, Dukes, EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993; 4(5): 353–365.
13. Reilly Associates. WPAI Scoring.[Internet] reillyassociates.net/WPAI_Scoring.html

Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Study title:	Interventional, randomized, double-blind, parallel-group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments
Study No.:	18898A
SAP date (v.1.0):	8 March 2021
SAP date (v.2.0):	13 October 2021

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

Authentication

[redacted] [redacted]

[redacted] [redacted]

Authorization

[redacted] [redacted]

Appendix II

Study Procedures and Assessments

Study Procedures and Assessments

Table 1 Study Procedures and Assessments

Visit Name	Screening	Baseline[e] + IMP	Phone Contact[k]	Phone Contact[k]	Primary Outcome + IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	Completion	Withdrawal[y]
	Placebo-controlled Period								Extension Period												
Visit Number	1	2	3	4	5	6	7	8[z]	9[z]	10[z]	11[z]	12	13	14	15	16	17	18	19	20	
End of Week[a]	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
Visit Window[b] (days relative to nominal visit)	-2		-2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+2	+2
Screening and Baseline Procedures and Assessments																					
Signed informed consents	√																				
Demographics (age, sex, race)	√																				
Diagnosis	√																				
Documented evidence of previous failure of 2-4 migraine preventive medications[c]	√																				
Disease-specific history	√																				
Relevant history (social, medical, psychiatric, neurological)	√																				
Recent medication	√	√																			
Smoking, alcohol consumption	√																				
Height	√																				
Blood sampling for serology (HIV, HBsAg, anti-HCV)	√																				

Visit Name	Screening	Baseline[e] + IMP	Phone Contact[k]	Phone Contact[k]	Primary Outcome + IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	Completion	Withdrawal[v]
	Placebo-controlled Period								Extension Period												
Visit Number	1	2	3	4	5	6	7	8[z]	9[z]	10[z]	11[z]	12	13	14	15	16	17	18	19	20	
End of Week[a]	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
Visit Window[b] (days relative to nominal visit)	-2		-2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+2	+2
Blood sampling for other screening (e.g., β-hCG, FSH)	√																				
Inclusion/exclusion criteria	√	√[f]																			
Signs and symptoms present at Screening and/or Baseline (before IMP intake) (recorded on an *Adverse Event Form*)	√	√																			
Randomization		√[d]																			
Efficacy Assessments (PROs)[g]																					
eDiary daily recording[h]																					v
eDiary data review and compliance check		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[v]
PGIC			√[l]		√			√			√			√			√			√	√[v]
MBS		√			√			√			√			√			√			√	√[v]
Pharmacoeconomic Assessments (PROs)[g]																					
HIT-6		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[v]
MSQ v2.1		√			√			√			√			√			√			√	√[v]
EQ-5D-5L		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[v]
HCRU		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[v]
WPAI		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[v]
Safety Assessments																					
Adverse events		√[m,n]	√	√	√[m,n]	√	√	√[m,n]	√	√	√[m,n]	√	√	√[m,n]	√	√	√[m,n]	√	√	√	√

Visit Name	**Screening**	**Baseline[e] + IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**Primary Outcome + IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**IMP**	**Phone Contact[k]**	**Phone Contact[k]**	**Completion**	**Withdrawal[v]**
	Placebo-controlled Period								**Extension Period**												
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[z]**	**9[z]**	**10[z]**	**11[z]**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	
Visit Window[b] (days relative to nominal visit)	**-2**		**-2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**+2**	**+2**
Blood and urine sampling for clinical safety laboratory tests	√	√[n]			√[n]			√[n]			√[n]			√[n]			√[n]			√	√
Blood ADA		√[n]			√[n]			√[n]			√[n]			√[n]			√[n]			√[p]	√
Vital signs body temperature including, weight, ECGs	√	√[n]			√[n]			√[n]			√[n]			√[n]			√[n]			√	√
Physical Examination	√	√[n]			√[n]			√[n]			√[n]			√[n]			√[n]			√	√
C-SSRS[o]	√	√			√			√			√			√			√			√	√
Biobanking																					
Blood sampling for gene expression profiling (RNA)[w]		√[n]			√[n]			√[n]						√[n]						√	√
Blood sampling for metabolomics/ proteomics (plasma)[w]		√[n]			√[n]			√[n]						√[n]						√	√
Blood sampling for pharmacogenetics (DNA) – optional[x]		√[n]																			
Blood sampling for possible future ADA assessment[y]								√[n]												√	√
Other Study Procedures and Assessments																					
IMP administered[r]		√[q]			√[q]			√[q]			√[q]			√[q]			√[q]				
IMP accountability[s]		√			√			√			√			√			√				
Concomitant medication (prescription and non-prescription)		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
eDiary training[i]	√																				

Visit Name	Screening	Baseline[e] + IMP	Phone Contact[k]	Phone Contact[k]	Primary Outcome + IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	IMP	Phone Contact[k]	Phone Contact[k]	Completion	Withdrawal[v]
	Placebo-controlled Period								Extension Period												
Visit Number	1	2	3	4	5	6	7	8[z]	9[z]	10[z]	11[z]	12	13	14	15	16	17	18	19	20	
End of Week[a]	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
Visit Window[b] (days relative to nominal visit)	-2		-2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+2	+2
PRO training[i]	√																				
eDiary closeout[j]																				√	√
Pregnancy test	√[t]	√			√			√			√			√			√			√	√
Exit Interview								√[u]													√[u]

ADA = anti-drug antibody; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = Euroqol 5 Dimensions; HBsAg = hepatitis B surface antigen; FSH = follicle-stimulating hormone; HCRU = Health Care Resource Utilization; βhCG = beta-human chorionic gonadotropin; HCV = hepatitis C virus; HIT-6 = Headache Impact Test; HIV = human immunodeficiency virus; IMP = investigational medicinal product; MBS = Most Bothersome Symptom; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire Version 2.1; PGIC = Patient Global Impression of Change; PRO = patient-reported outcome; WPAI = Work Productivity and Activity Impairment questionnaire

a All assessments (except for the requirement of screening assessments prior to the Baseline Visit) may be completed over a maximum of 2 consecutive days with the exception of PROs (see footnote g below); if so, the first day is considered the "visit" day according to the schedule.

b 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.

c The patients must have documented evidence of failure in the past 10 years of 2-4 different pharmacological migraine preventive medications. Acceptable documentation of previous treatment failures includes medical or pharmacy record or physician's confirmation specific to each treatment.

d Randomization will occur at the Baseline Visit 28-30 days after the Screening Visit and after eligibility criteria are confirmed by the investigator.

e Dosing must occur at the Baseline Visit.

f Inclusion and exclusion criteria review must be done prior to dosing at the Baseline Visit.

g Assessments involving interviews and scales must be done before the infusions. All efficacy and pharmacoeconomic assessments are PROs. PROs 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. Additionally, PGIC (at Week 4 only), HIT-6, EQ-5D-5L, HCRU, WPAI 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.

h The eDiary assessments will be completed in the remote setting on a daily basis.

i At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary and training of efficacy and pharmacoeconomic assessments (PROs). Details will be provided in a separate user manual.

j The eDiary closeout will take place at the Completion/Withdrawal Visit, while the patient is at site. Details will be provided in a separate user manual.

k The patients will be contacted via phone every 4 weeks between infusion visits for eDiary data review and compliance check, to ensure that selected assessments have been completed and for collection of relevant information such as AEs and concomitant medication.

l PGIC at Week 4 must be completed in the remote setting.

m At infusion visits, IRRs must be checked as part of the overall AE collection, after infusion and before the patient is discharged from the site.

n At infusion visits, physical examination, ECG, blood sampling (for clinical safety laboratory tests, ADA and biobank) and urine samples (for clinical safety laboratory tests and pregnancy) must be conducted before infusion. AEs, vital signs including body temperature should be checked before and after infusion.

o The C-SSRS will be administered by the authorized rater at the clinic and prior to infusion.

p Patients who test positive for ADA at the Completion will be asked to provide up to two additional blood samples for immunogenicity testing at 12-week intervals for up to 24 weeks.

q At infusion visits, patients must be monitored for a period of 1 hour from the end-of-infusion. Patients will be requested to stay longer should the investigator determine this is clinically warranted.

r An unblinded pharmacist or designee is responsible for receiving, storing and preparing IMP. The pharmacist or designee will not be responsible for other aspects of the clinical trial where blinding is necessary.

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

t Pregnancy test at Screening to be conducted using serum β-HCG and at all other visits using urine testing.

u *Exit Interview subset*: Patients undergoing the exit interviews must provide signed subset-specific Informed Consent. The exit interview will be conducted at the Week 24 Visit or at the Withdrawal Visit for patients withdrawing prior to Week 24. The exit interview must be conducted after all visit assessments are completed. Details will be provided in a separate exit interview guide.

v Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit 12 weeks after the last dose of IMP and undergo Safety Follow-Up evaluations. Patients who withdraw prior to Week 24 will undergo additional Efficacy Follow-Up evaluations.

w Exploratory gene expression profiling (RNA) and metabolomics/proteomics are an integrated part of the study and are covered by the main Informed Consent.

x Sampling for pharmacogenetics is optional and a separate signed Informed Consent must be in place to cover this analysis.

y Whole blood samples for serum separation and potential future ADA analyses will be drawn at the Baseline Visit and at Week 24.

z If a decision is made to end enrolment early, patients who have not yet completed their Week 12 Visit will immediately transfer to the Extension Period. Patients originally randomized to placebo will be scheduled for Visit 8 immediately and active treatment will be initiated. Patients originally randomized to eptinezumab will be scheduled for Visit 9 or 10 or 11. For these patients, the scheduling of Visit 9 or 10 or 11 should allow for the next dose of IMP to be received at Visit 11, that is 12 weeks after their first dose. Patients who have already completed their Week 12 Visit will continue to finalise 24 weeks of treatment in the Placebo-controlled Period and enter the Extension Period at Visit 8. Patients must continue to complete the daily headache eDiary during the transfer to the Extension Period.

Appendix III
PDS Migraine Event Definition

PDS Migraine Event Definition

The PDS definition of a migraine day, which was used at randomization for the classification into EM and CM stratum as defined in inclusion criterion 10, is a day with a migraine event defined as:

Table 2 PDS Migraine Event Definition

6.1.6	Migraine **Event** Definition	3.3.2	**Any reported headache (Duration ≥ 30 minutes) that meets <u>all 3</u> of the following criteria:** 1. Duration: a. ≥ 4 hours OR b. ≥ 30 minutes AND < 4 hours AND subject took medication because they believed they were experiencing a migraine. 2. Had at least 2 of the following a. Unilateral location b. Pulsating quality c. Moderate or Severe pain intensity d. Aggravation by or causing avoidance of routine physical activity 3. Had at least 1 of the following a. Nausea b. Vomiting c. Photophobia AND Phonophobia

See PDS for details regarding the definitions and calculations used for eligibility.

Appendix IV
SAS® Code

SAS® Code

Primary Analysis

The SAS® code for the primary analysis of the primary endpoint described in Section 12.3.2 is given below. Here, it is assumed that the ordering of the levels of the treatment factor is: 100 mg, 300 mg, placebo.

```
proc mixed data = xxxx method = REML;
    class USUBJID TRTP(ref = 'Placebo') STRATUM COUNTRY AVISITN;

    model CHG = BASE TRTP AVISITN STRATUM COUNTRY BASE*AVISITN
                STRATUM*AVISITN TRTP*AVISITN / DDFM = KR;

    repeated AVISITN / subject = USUBJID type = UN;

    lsmestimate TRTP*AVISITN "100 mg vs. Placebo, Weeks 1-12"
                [1, 1 1] [1, 1 2] [1, 1 3] [-1, 3 1] [-1, 3 2] [-1, 3 3]/
                divisor = 3 cl;

    lsmestimate TRTP*AVISITN "300 mg vs. Placebo, Weeks 1-12"
                [1, 2 1] [1, 2 2] [1, 2 3] [-1, 3 1] [-1, 3 2] [-1, 3 3]/
                divisor = 3 cl;

run;
```

Key Secondary Analysis

The SAS® code for conducting the key secondary analyses described in Section 12.4.2 is given below. Note that p-values to be included in the test strategy will be computed from a likelihood ratio test.

```
proc logistic data = xxxx;
       by AVISITN;
       class TRTP(ref = "Placebo") STRATUM / param = GLM;
       model RESPONSE(event = "1") = TRTP STRATUM BASE /
                                                clodds = PL alpha = 0.05;
run;
```

Secondary Analysis

The SAS® code for computing p-values from the extended CMH test for the secondary endpoints described in Section 12.5 is given below. The p-values are computed separately for each active treatment group. In the code below the relevant p-value is stored in the `p_value` output data set.

```
proc freq data = xxxx (where = (TRTP in ('EPTI xxx mg' 'PBO') and AVISIT =
'xxxx'));
   output out = p_value CMHRMS;
```

```
   tables STRATUM*TRTP*AVAL / cmh2;
run;
```

Sensitivity Analysis (placebo-based Multiple Imputation)

The SAS® code that will be the basis for the placebo-based multiple imputation (pMI) sensitivity analysis for the key secondary endpoint, HIT-6, mentioned in Section 12.4.4, is given below. Note that data transformation steps are omitted and only the most crucial parts are shown.

The procedure for the pMI method will include the following steps:

1. Impute missing intermittent data using Markov Chain Monte Carlo (MCMC) methodology by treatment group with the model for HIT-6 total score at baseline and at Week 4, 8, 12, 16, 20, and 24, using PROC MI from SAS®, with seed = 101990 and 200 imputations, to impute data to a monotone missing data pattern under a MAR assumption.
2. At time t, perform pMI according to the placebo-treated patients, where the monotone missing values are assumed to follow an MNAR pattern. Only observations up to time t will be included for the placebo group. Based on the model established using only placebo data, observations up to but not beyond time t-1 in the eptinezumab treatment groups will be used for imputing the missing data at time t. The regression model will include stratum and observed or imputed outcomes up to time t (including the baseline scores), and will use the MONOTON REG option in PROC MI with seed = 88775.
3. Assemble a dataset containing data for all patients, including the imputed data from time t, to serve as predictors for the imputation of the next visit.
4. Repeat steps 2 to 3 sequentially over all visits (t+1, t+2…).
5. Analyse the 200 complete datasets using the same MMRM model as described in Section 12.4.2.
6. Combine the estimated treatment effects obtained across the imputed datasets using PROC MIANALYZE from SAS®.

In the below, it is assumed that:
transposed_data: transposed analysis data with each AVISITN as a separate variable
mono_data: data with monotone missing data pattern
imputed_data: data with missing values imputed
mmrm_data: data with CHG calculated from imputed values and with additional variables to be used in the modelling added
diff_data: data with estimated treatment differences from the converged models fit on each of the 200 datasets
results_data: data with the combined estimated treatment effects

Code parts:

```
*Impute intermittent missing values;
```

```
proc mi data = transposed_data out = mono_data nimpute = 200 seed = 101990;
   by TRTP;
   var BASE AVISITN_3 AVISITN_4 AVISITN_5 AVISITN_6 AVISITN_7 AVISITN_8;
   mcmc chain = multiple
   impute = monotone;
run;

*Impute monotone missing values;
proc mi data = mono_data seed = 88775 nimpute = 1 out = imputed_data;
    by  IMPUTATION ;
    class STRATUM TRTP;

    monotone regression;
    mnar model(AVISITN_3 AVISITN_4 AVISITN_5 AVISITN_6 AVISITN_7 AVISITN_8 /
         modelobs = (TRTP = "PBO"));
    var STRATUM BASE AVISITN_3 AVISITN_4 AVISITN_5 AVISITN_6 AVISITN_7
        AVISITN_8;
run;

*Execute model on imputed data;
ods output lsmeans =   LS01 diffs =   D01 ConvergenceStatus = __CONV01;
proc mixed data = mmrm_data method = REML;
    by _IMPUTATION_;

    class AVISITN COUNTRY STRATUM TRTP USUBJID;
    model CHG = BASE TRTP AVISITN STRATUM COUNTRY BASE*AVISITN
                STRATUM*AVISITN TRTP*AVISITN / DDFM = KR;

    lsmeans TRTP*AVISITN / diff cl alpha = 0.05;
    repeated AVISITN / subject = USUBJID type = un;
run;

*Combine model estimates;
proc mianalyze parms(classvar = full) = diff_data;
       by AVISITN;
       class TRTP;
       modeleffects TRTP*AVISITN;
       ods output ParameterEstimates = results_data;
run;
```

Appendix V
PCS Criteria

PCS Criteria

Table 3 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	U/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	U/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	U/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	U/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.		≥ 0.065
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	U/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 4 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 5 PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS Low	PCS High
Absolute Time Interval				
PR interval	PRAG	Msec		≥ 260
QRS interval	QRSAG	Msec		≥ 150
QT interval	QTAG	Msec		≥ 500
Derived Time Interval				
Heart rate	EGHRMN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCBAG	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCFAG	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value.

Appendix VI
Adverse Events of Special Interest

Adverse Events of Special Interest

Table 6 Adverse Events of Special Interest

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

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