H. Lundbeck A/S

Statistical Analysis Plan

Protocol Numbers	18903A
Investigational Product	Eptinezumab (Lu AG09221)
Sponsor	H. Lundbeck A/S Ottiliavej 9 2500 Valby Denmark
Date of SAP (Version 3.0)	04AUG 2020

SIGNATURE PAGE

Statistical Analysis Plan Version 3.0

The document has been signed by the individuals listed below.

Issued by:

CCI

CCI

CCI

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LIST OF ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BMI	Body Mass Index
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eDiary	Electronic Diary
HIT-6	Headache Impact Test
kg	Kilogram
kg/m^2	Kilogram per Meter Squared
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MOH	Medication Overuse Headache
MTOQ-6	Migraine Treatment Optimization Questionnaire-6
NSAID	Non-steroidal anti-inflammatory drug
PCS	Potentially clinically significant

PGIC	Patient Global Impression of Change
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal

1. INTRODUCTION

This is a parallel group, double-blind, randomized, placebo-controlled study assessing the efficacy of eptinezumab for acute migraine, as defined as an active intercurrent migraine occurring in those patients who are candidates for preventive therapy. The patients randomized to the eptinezumab treatment group will receive an IV infusion of eptinezumab and the patients randomized to placebo will receive an IV infusion of placebo. See study protocol Section 9 for more details on the study drug.

Section 5 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with eptinezumab. The purpose of this Statistical Analysis Plan (SAP) is to define the methodology for analyzing and summarizing the data collected during the conduct of Study 18903A, previously ALD403-CLIN-015. The study will be referenced as 18903A throughout this document.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on 18903A (previously ALD403-CLIN-015) Protocol including Amendment 2 dated 06DEC2019 and case report forms (CRFs) approved 15OCT2019. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of the study is: To evaluate the effect of eptinezumab compared to placebo with respect to time to headache pain freedom AND time to absence of most bothersome symptom during an intercurrent migraine that occurs in subjects who are candidates for preventive therapy.

2.2.2. Secondary Objectives

The secondary objectives of the study are to evaluate the efficacy of eptinezumab vs. placebo on:

- Headache pain freedom at timepoints up to 48 hours
- Absence of most bothersome symptom at timepoints up to 48 hours
- Time to headache pain relief
- Sustained headache pain freedom from 2 – 48 hours

- Acute rescue medication use
- Effect on symptoms of the qualifying migraine
- Effect on patient-reported outcomes

2.3. Study Endpoints

2.3.1. Co-Primary Endpoints

- Time to headache pain freedom
- Time to absence of most bothersome symptom

2.3.2. Key Secondary Endpoints

- Headache pain freedom at 2 hours
- Absence of most bothersome symptom at 2 hours

2.3.3. Secondary Endpoints

- Absence of headache pain at 4 hours
- Absence of most bothersome symptom at 4 hours
- Use of rescue medication within the first 24 hours

2.3.4. Exploratory Endpoints

- Time to headache pain relief
- Heachache pain relief at 2 hours
- Heachache pain relief at 4 hours
- Headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours
- Use of rescue medication within the first 48 hours
- Absence of photophobia at all timepoints
- Absence of phonophobia at all timepoints
- Absence of nausea at all timepoints
- Change from Baseline in Headache Impact Test (HIT-6) at Week 4
- Change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4
- Absence of headache pain at all timepoints other than 2 and 4 hours

- Patient Global Impression of Change (PGIC) at Week 4
- Time to next migraine
- Time to first rescue medication

2.3.5. Safety Endpoints

- Adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

3. STUDY DESIGN

3.1. Study Design Description

The total study duration will be approximately 4 to 12 weeks, including up to 8-week screening period, with clinic visits occurring on Screening, Day 0 (dosing day), and Week 4. See Table 2 and Table 3 for schedules of events and assessments for the whole study and for Day 0 through 48 hours.

Randomization and dosing will be triggered by a qualifying migraine and will occur on Day 0. Study design requires that study drug administration be initiated within 1 to 6 hours of migraine onset, and subjects must be willing and able to travel to the site for study drug administration within this time frame. Subjects must remain at the site for 4-hours post start-of-infusion for observation. Subjects may be followed longer than 4 weeks, if necessary, for safety follow-up as described in the protocol. An eDiary will be assigned prior to dosing at the Day 0 visit and dosed subjects must complete the eDiary at prescribed timepoints (just before infusion, and after 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, and 48 hours post start of infusion) through 48 hours after start of infusion (t=0). Additionally, subjects will complete daily eDiary data entry from Day 3 until a new migraine is reported.

3.2. Randomization

Subjects will be randomized to receive either 100 mg eptinezumab or placebo in a 1:1 ratio. Randomization will be stratified by concomitant migraine preventative treatment (concomitant migraine preventative treatment use vs. no concomitant migraine preventative treatment use) and region (North America vs. Rest of World).

3.3. Sample Size Considerations

The planned sample size for this study is 450 randomized and dosed subjects. These subjects will be allocated into 2 treatment groups, eptinezumab vs. placebo, in a 1:1 ratio. Two hundred twenty-five subjects per group provides at least 90% power to detect a 0.736 hazard ratio favouring eptinezumab at the 5% significance level for both co-primary endpoints. Based on simulations, it has been shown that this sample size also provides 90% power for the key secondary endpoints, assuming a rate of 20% for the placebo group and a rate of 34.5% for the eptinezumab group, i.e. that eptinezumab increases response rates for both 2-hour endpoints by at least 14.5 percentage points at a 5% significance level, where the correlation between the two endpoints is assumed to be 0.8.

3.4. Multiplicity

To show effect on the co-primary endpoints, it is required to achieve statistical significance on a 5% significance level simultaneously for both of the primary endpoints, and therefore no multiplicity adjustment is done for the primary endpoints. If both co-primary endpoints achieve statistical significance at a 5% significance level, the key secondary endpoints will be tested hierarchically at a 5% significance level. First the pain freedom at 2 hours will be tested at a 5% significance level and if a statistically significant effect is seen, testing will continue with the absence from most bothersome symptom at 2 hours at a 5% significance level. If both key secondary endpoints achieve statistical significance, the secondary endpoints will be tested hierarchically at an overall 5% level of significance. First absence of headache pain at 4 hours will be tested at 5% level of significance, and if statistically significant, the absence of the most bothersome symptom at 4 hours will be at 5% level of significance. If also the second test is statistically significant, the use of rescue medication within the first 24 hours will be tested at 5% level of significance. All tests will be 2-sided.

All other endpoints will use a 2-sided 5% significance level with no adjustment for multiplicity. If the hierarchical testing strategy is stopped at any stage due to insignificant results, the remaining key secondary and/or secondary endpoints will not be part of the formal testing, but nominal p-values will be presented.

4. STATISTICAL METHODOLOGY

4.1. General Methodology

Unless otherwise stated, SAS®software Version 9.4 or later will be used for the generation of all tables, graphs, and statistical analyses. SAS® code for performing the analyses of the co-primary and key secondary endpoints can be found in Appendix II.

For all efficacy endpoints, summary tables with descriptive statistics will be included taking into account the type of endpoint as outlined below. For some endpoints, the summary tables are further described in the sections related to the specific endpoint.

Summary statistics including the number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Generally, the minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

For time-to-event endpoints, the descriptive statistics that will be presented are the number of patients included in the analysis, the number of patients that experienced an event, and a table displaying for each timepoint where events occurred, how many patients were at risk and how many patients experienced an event at the timepoint.

For binary endpoints, crosstables will be presented displaying the number and percentage of patients in each treatment group that fulfill the definition related to the specific endpoint.

Summary statistics will be reported based upon observed data. For statistical analysis purposes, rules for handling missing data will be applied and these are described in the following sections.

For AEs, medical history and concomitant medications reported on a per-subject basis, the denominator for the percentage calculation will be the number of subjects at risk in each treatment group. A subject will be considered at risk if the subject is in the analysis set and in the subgroup of interest.

All nominal p-values will be based on 2-sided tests. See Section 3.4 for description of the significance levels used.

If a p-value is less than 0.0001 it will be displayed as “< 0.0001”. All p-values larger than 0.0001 will be rounded to 4 decimal places.

4.2. Analysis Populations

The analysis populations are defined as the following:

- Full Analysis Population (FAP) – Includes all randomized subjects who received eptinezumab or placebo. Subjects will be summarized within the treatment group to which they were randomized. This population will be used for all efficacy analyses.
- Safety Population – Includes all subjects who received eptinezumab or placebo. Subjects will be summarized within the treatment group for which they actually received treatment. This population will be used for the safety analyses.

4.3. Statistical Methods for Efficacy Analyses

4.3.1. Co-Primary Efficacy Endpoints

Hypothesis testing will be performed for the co-primary endpoints:

- Time to headache pain freedom
- Time to absence of most bothersome symptom (MBS)

4.3.1.1. Primary Estimands

In line with the recently released addendum to the ICH E9 guideline on estimands and sensitivity analysis in clinical trials[1], descriptions of the primary and key secondary estimands are included in this document.

To further clarify the estimands, estimand attributes (treatment condition of interest, the population of interest, the variable that will be used to address the clinical question, and the population-level summary for the variable) will be included. Furthermore, a description of the potential intercurrent events that may affect the clinical question of interest and the strategy used to handle the intercurrent events will be included.

4.3.1.1.1. Intercurrent Events

Potential intercurrent events occurring after treatment initiation that affect the interpretation of the primary endpoints include use of rescue medication, sleep, and death.

Given the duration of the study and the population included, no deaths are expected. Therefore, handling of death as an intercurrent event will not be pre-specified.

Sleep may have a beneficial effect on migraine. During the 48 hours of data collection of the primary endpoints, sleep will only be collected indirectly via the collection of whether the patient was asleep or awake at the timepoints where pain and MBS symptom status are collected. This is insufficient to address the impact of sleep as an intercurrent event on the ongoing migraine.

In this study, rescue medication is defined as

- Medication use collected through the eDiary that is taken after start of infusion

It is expected that the majority of the rescue medications used in the study will belong to one of the following 3 categories: Triptans, NSAIDs, and analgesics. These are all characterized by potentially working fast and having an immediate effect on pain as well as all 3 types of MBS. This implies that the status of the patient after use of rescue medication could be a consequence of the rescue medication rather than a result of the randomized treatment. Since the effect of interest is the pharmacological effect of eptinezumab, this intercurrent event will be addressed using a hypothetical strategy by disregarding information obtained after the use of rescue medication. The hypothetical scenario that is envisaged is one where rescue medication is not available.

4.3.1.1.2. Estimands

The clinical question of interest is whether pain freedom and absence of MBS can be achieved faster with eptinezumab than with placebo.

The primary estimands defined to answer this question are the following:

- The hypothetical effect of eptinezumab on time to pain freedom that would be seen in a population where no rescue medication was available
- The hypothetical effect of eptinezumab on time to absence of MBS that would be seen in a population where no rescue medication was available

The estimand attributes are as follows:

Treatment condition of interest

The treatment condition of interest is eptinezumab 100 mg compared to placebo for both primary estimands.

Population

The population for both primary estimands is the entire study population that is, subjects who are candidates for preventive therapy defined by fulfilling the inclusion and exclusion criteria.

Variables

Headache pain will be collected on a 4-point scale with 3 being severe, 2 being moderate, 1 being mild, and 0 being no pain.

MBS is the symptom from among nausea, photophobia (light sensitivity), or phonophobia (sound sensitivity) that has been identified by the patient on Day 1 prior to dosing as being the most bothersome one for the migraine being treated.

The patient is asked to report headache pain and whether each of the 3 symptoms are present at specified time points after the infusion.

For the primary estimands, the variables that address the clinical question of interest are the following:

- Time to pain freedom. The time is calculated from the start of infusion to the first time point post infusion with a rating of no pain, within the first 48 hours after infusion start
- Time to absence of MBS. Time is calculated from the start of infusion to the first time point post infusion where absence of MBS is recorded, within the first 48 hours after infusion start

Intercurrent Events

The intercurrent event of taking rescue medication prior to obtaining pain freedom/absence of MBS will be addressed using a hypothetical strategy by disregarding information obtained after the use of rescue medication. No other intercurrent events will be addressed.

Population level summary

The population level summary for both variables defined above will be the hazard ratio (HR) between eptinezumab and placebo.

4.3.1.1.3. Primary Analysis

The two co-primary endpoints will be analyzed similarly but separately and the analyses will be based on the FAP.

The endpoints are collected at the following pre-specified timepoints: Just before infusion, and after 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, and 48 hours post start of infusion, see also Table 3.

For conducting the analyses, the following derivations will apply to each of the endpoints:

- If a patient reports pain freedom/absence of MBS without having reported use of rescue medication up to and including the timepoint where pain freedom/absence of MBS is reported, the first collected timepont of pain freedom/absence of MBS will be used for analysis (status indicator equals 1, indicating pain freedom obtained)
- If a patient reports taking rescue medication without having reported pain freedom/absence of MBS at an earlier timepoint, the timepoint of first rescue medication reporting is the value that will be used in the analysis (status indicator equals 0, indicating censoring at the time of rescue medication)

- If a patient does not report pain freedom/absence of MBS during the 48 hours and does not report taking rescue medication at any timepoint, the timepoint of the last entry in the eDiary for the 48 hours will be used in the analysis (status indicator equals 0, indicating administrative censoring)

Summary tables as described in section 4.1 will be provided for each treatment group for both co-primary endpoints.

The HR for time to headache pain freedom/time to absence of MBS between eptinezumab and placebo, will be estimated from a stratified Cox proportional hazards model with a single treatment covariate and using Efron's method of tie handling. The stratification factors will be identical to the factors used for randomization.

The HR will be reported together with its 95% confidence interval. The confidence interval will be computed from the profile likelihood. The median estimate for time to pain freedom/absence of MBS for each treatment group from the stratified Cox model will also be reported. For computing median estimates of time to pain freedom/time to absence of MBS for each treatment group, the estimated survival curves from the Cox model for each stratum will be combined using a weighted average of the curves for each stratum. The weights will equal the number of patients in the stratum divided by the total number of patients included in the analysis. Plots of the combined survival curves across strata from the stratified Cox model will be presented by treatment group, as well as plots of the estimated survival curves from the stratified Cox model by stratum and treatment group.

The likelihood ratio test from this model, testing whether the hazard ratio between the two treatments equals 1 (whether the parameter for the treatment effect is equal to 0) will be used for testing whether there is an advantage of the eptinezumab treatment over placebo.

Kaplan-Meier plots for time to pain freedom and time to absence of MBS will be presented for each treatment group.

SAS® code for the primary analyses is given in Appendix II.

4.3.2. Key Secondary Efficacy Endpoints

Hypothesis testing will be performed for the key secondary endpoints:

- Headache pain freedom at 2 hours
- Absence of most bothersome symptom at 2 hours

4.3.2.1. Key Secondary Estimands

Like for the co-primary endpoints, estimands related to the key secondary endpoints will be described.

4.3.2.1.1. Intercurrent Events

For the key secondary endpoints, the potential intercurrent event: use of rescue medication is expected to happen only in a limited number of instances prior to observing the key secondary endpoints after 2 hours, as the protocol requests that no rescue medication is taken prior to 2 hours. But as the occurrence might have a substantial impact on the endpoints, it will still be considered.

Since the use of rescue medication prior to the 2-hour assessments could result in considerable improvement that would not be due to the randomized treatments, a composite strategy will be used to address this intercurrent event for the key secondary endpoints. Thus, to obtain the result of either pain freedom or absence of MBS at 2 hours, it is required to do so without prior use of rescue medication.

4.3.2.1.2. Estimands

The clinical question of interest is whether more patients experience pain freedoom and absence of MBS after two hours post infusion with eptinezumab than with placebo.

The key secondary estimands defined to answer this question are the following:

- The effect of eptinezumab on number of patients obtaining pain freedom at 2 hours post start of infusion without the use of rescue medication
- The effect of eptinezumab on number of patients obtaining absence of MBS at 2 hours post start of infusion without the use of rescue medication

The estimands' attributes are as follows:

Treatment condition of interest

The treatment condition of interest is eptinezumab 100 mg compared to placebo for both key secondary estimands.

Population

The population for both key secondary estimands is the entire study population that is, subjects who are candidates for preventive therapy defined by fulfilling the inclusion and exclusion criteria.

Variables

For the key secondary estimands, the variables that address the clinical question of interest are the following:

- Binary response variable indicating a successful response if a patient achieves headache pain freedom at 2 hours post start of infusion without any prior administration of rescue medication

- Binary response variable indicating a successful response if a patient achieves absence of MBS at 2 hours post start of infusion without any prior administration of rescue medication

Intercurrent events

As the intercurrent event of use of rescue medication has been addressed directly in the definition of the composite endpoint, there are no other intercurrent events to address.

Population level summary

The population level summary for both variables defined above will be the difference in response proportions between treatment conditions (eptinezumab and placebo).

4.3.2.1.3. Key Secondary Analysis

The two key secondary endpoints will be analyzed similarly but separately, and the analyses will be based on the FAP.

Obtaining headache pain freedom at 2 hours is defined as having a measurement at 2 hours, and not having pain at 2 hours, and not taking rescue medication prior to or at the 2 hours assessment. All other patients are considered to not have obtained pain freedom at 2 hours. The endpoint of obtaining absence of MBS at 2 hours is similarly defined.

For each of the two key secondary endpoints, the treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test, adjusting for the study's stratification factors; concomitant migraine preventive treatment use and region.

The Mantel-Haenszel estimate of the common odds ratio and associated confidence intervals will be provided.
Furthermore, the difference in rates and associated confidence interval will be calculated based on the normal approximation of two independent proportions without taking the stratification factors into account.

SAS® code for the key secondary analyses is given in Appendix II.

Plots of the proportion of patients achieving pain freedom and absence of their MBS across time (baseline, 0.5 hours, 1 hour, 1.5 hours and 2 hours), for each treatment group, will be produced. If the pain or MBS assessment is missing at a given timepoint, it is assumed that no pain freedom or no absence of MBS has been obtained for this timepoint.

4.3.3. Secondary Efficacy Endpoints

The absence of headache pain (headache pain freedom) at 4 hours, and the absence of most bothersome symptom at 4 hours will be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3. The analyses will be based on the FAP unless otherwise specified.

Use of rescue medication by 24 hours is defined as having a measurement of use of rescue medication within the first 24 hours. In case of a missing assessment, it will be assumed that no rescue medication was taken in connection with that assessment. The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 using the definition above.

4.3.4. Exploratory Efficacy Analyses

All exploratory efficacy endpoints will be assessed descriptively or tested at a 2-sided 5% alpha with no adjustment for multiplicity and be based on the FAP.

Time to headache pain relief

Headache pain relief is defined as a rating of mild or no pain (rating of 1 or 0). Time to headache pain relief is defined similarly to the time to headache pain freedom, i.e. time from start of infusion to the first timepoint post infusion with pain relief, within the first 48 hours after infusion start.

Handling of rescue medication and missing timepoints will be done according to the rules for the co-primary endpoints defined in section 4.3.1.1.3.

Time to headache pain relief will be analysed similarly to the two co-primary endpoints described in section 4.3.1.1.3.

Headache pain relief at 2 and 4 hours

Headache pain relief at 2 and 4 hours post-dose will be assessed using 4-point Likert scale, where patients report a pain level of mild or no pain (rating of 1 or 0) at 2 and 4 hours post-dose, respectively.

The endpoints will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 using the definition above.

Headache pain freedom at 2 hours with sustained headache pain freedom for 24 hours

Obtaining headache pain freedom at 2 hours with sustained headache pain freedom for 24 hours is defined as having an available measurement at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours, and not having pain at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours, and not taking rescue medication prior to or at the 24 hours assessment. All other patients are considered to not have headache pain freedom at 2 hours with sustained headache pain freedom for 24 hours.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 using the definition above.

Headache pain freedom at 2 hours with sustained headache pain freedom for 48 hours

Obtaining headache pain freedom at 2 hours with sustained headache pain freedom for 48 hours is defined as having an available measurement at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 6 hours, 9 hours, 12 hours, 24 hours, and 48 hours, and not having pain at 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 6 hours, 9 hours, 12 hours, 24 hours, and 48 hours, and not taking rescue medication prior to or at the 48 hours assessment. All other patients are considered to not have headache pain freedom at 2 hours with sustained headache pain freedom for 48 hours.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 using the definition above.

Use of rescue medication by 48 hours

Use of rescue medication by 48 hours is defined as having a measurement of use of rescue medication within the first 48 hours. In case of a missing assessment, it will be assumed that no rescue medication was taken in connection with that assessment.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 using the definition above.

Absence of photophobia (light sensitivity) at all timepoints

The subgroup of patients with photophobia (light sensitivity) is defined as the subgroup of patients in the FAP who answer 'Yes' to the eDiary question "Do you have light sensitivity?" at baseline. The absence of photophobia will be presented for each timepoint separately.

Absence of photophobia at X hours is defined as having a record of no photophobia at X hours and not taking rescue medication prior to or at the X-hour assessment. All other patients are considered not to have obtained the endpoint.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3, but only for the sub-population of patients with photophobia at baseline.

In addition, cross tables displaying the number and percentage of patients with or without photophobia at baseline that do or do not experience photophobia will be presented for each treatment group and timepoint based on the full FAP.

Absence of phonophobia (sound sensitivity) at all timepoints

The subgroup of patients with phonophobia (sound sensitivity) is defined as the subgroup of patients in the FAP who answer 'Yes' to the eDiary question "Do you have sound sensitivity?" at baseline. The absence of phonophobia will be presented for each timepoint separately.

Absence of phonophobia at X hours is defined as having a record of no phonophobia at X hours and not taking rescue medication prior to or at the X-hour assessment. All other patients are considered not to have obtained the endpoint.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3, but only for the sub-population of patients with phonophobia at baseline.

In addition, cross tables displaying the number and percentage of patients with or without phonophobia at baseline that do or do not experience phonophobia will be presented for each treatment group and timepoint based on the full FAP.

Absence of nausea at all timepoints

The subgroup of patients with nausea is defined as the subgroup of patients in the FAP who answer 'Yes' to the eDiary question "Do you have nausea?" at baseline. The absence of nausea will be presented for each timepoint separately.

Absence of nausea at X hours is defined as having a record of no nausea at X hours and not taking rescue medication prior to or at the X-hour assessment. All other patients are considered not to have obtained the endpoint.

The endpoint will then be analysed similarly to the key secondary endpoints described in section 4.3.2.1.3 but only for the sub-population of patients with nausea at baseline.

In addition, cross tables displaying the number and percentage of patients with or without nausea at baseline that do or do not experience nausea will be presented for each treatment group and timepoint based on the full FAP.

Change from Baseline in Headache Impact Test (HIT-6) at Week 4

The Headache Impact Test (HIT) is a tool used to measure the impact and effect on the ability to function normal in daily life when a headache occurs. The HIT is a 6 question, Likert-type, selfreporting questionnaire with responses ranging from "Never" to "Always" with the following response scores: Never=6, Rarely=8, Sometimes=10, Very Often=11, Always=13. The total score for the HIT is the sum of each response score and will be treated as missing if the response is missing for one or more questions. The HIT total score ranges from 36 to 78, with score ranges having the following life impact:

Score Range	Life Impact
>=60	Severe
56-59	Substantial
50-55	Some
<=49	Little to None

The actual score and change from baseline for the total score will be summarized at each scheduled visit by treatment group. A shift from baseline to the week 4 visit by treatment group will be tabulated for each item.

An Analysis of Covariance (ANCOVA) model will be used to test for a difference between treatment arms for the total score. **Error! Reference source not found.**The model will include the HIT-6 change from baseline measure at Week 4 as the response variable. Baseline value, treatment group and the stratification variables concomitant treatment (use vs. no use) and region (North America vs. Rest of World) will be the independent variables.

In addition, a similar ANCOVA will be fitted for each individual item.

In the analyses, the value from the week 4 visit will be used, regardless of whether it is an actual week 4 assessment or an early termination assessment. In case of any unscheduled assessments of HIT-6, the latest post-baseline value will we used.

Change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4

The migraine treatment optimization questionnaire-6 (mTOQ-6) is a tool used to assess response to acute treatment in persons with migraine. The mTOQ-6 is a 6 question, Likert-type, self-reporting questionnaire with responses ranging from “Never” to “Half The Time Or More” with the following response scores: Never=1, Rarely=2, Less Than Half The Time=3, Half The Time Or More=4. The total score for the mTOQ-6 is the sum of each response score and will be treated as missing if the response is missing for one or more questions. The mTOQ total score ranges from 6 to 24.

The actual score and change from baseline for the total score will be summarized at each scheduled visit by treatment group A shift from baseline to the week 4 visit by treatment group will be tabulated for each item.

An ANCOVA model will be used to test for a difference between treatment arms for the total score. This model will include the mTOQ-6 change from baseline measure at Week 4 as the response variable. Baseline value, treatment group and the stratification variables concomitant treatment (use vs. no use) and region (North America vs. Rest of World) will be the independent variables.

In the analysis, the value from the week 4 visit will be used, regardless of whether it is an actual week 4 assessment or an early termination assessment. In case of any unscheduled assessments of mTOQ-6, the latest post-baseline value will we used.

Headache Pain Freedom at all Timepoints

The analysis of headache pain freedom (denoted absense of headache pain in section 2.3.4) at all timepoints other than 2 and 4 hours will be analysed similarly to the key secondary endpoint of headache pain freedom described in section 4.3.2.1.3.

Time to next migraine

Time to next migraine is defined as the first day, beginning from Day 3, at which the subject reports a new migraine. The time will be calculated as:

Time to next migraine = Date of new migraine – date of Day 3

and will be censored at the time of the last entry of the subject.
The analysis of the time to next migraine will be perfomed similarly to the analysis of the co-primary endpoints described in section 4.3.1.1.3 as applicable.

PGIC at Week 4

The frequency distribution of PGIC responses will be summarized.

Time to First Rescue Medication

An exploratory analysis will be performed assessing time to first rescue medication. Similarly to the primary endpoints, time will be calculated from the start of infusion to the first time point post infusion where the patient answers "Yes" to the eDiary question "Have you taken any medication(s) to treat your migraine symptom(s) or pain since you last entered data in the eDiary?", using the nominal timepoints for eDiary collection. Furthermore, the following derivations will apply:

- If a patient reports use of rescue medication, the timepoint of first rescue medication registration will be used in the analysis (status indicator equals 1, indicating rescue medication used)
- If a patient does not report any rescue medication use during the 48 hours, the timepoint of the last entry in the eDiary for the 48 hours will be used in the analysis (status indicator equals 0, indicating administrative censoring)

The analysis will then be conducted similarly to the primary analysis described in section 4.3.1.1.3.

4.3.5. Sensitivity Analyses

The following sensitivity analyses will be performed for each of the three time to event efficacy endpoints: time to headache pain freedom, time to absence of MBS, and time to pain relief.

Rescue Medication

An analysis similar to the primary analysis will be conducted, where the rescue medication censoring is removed. This means that a patient's time value will be censored only if a patient does not report pain freedom/absence of MBS/pain relief at all during the 48 hours.

Persistence

An analysis similar to the primary analysis will be conducted, where an event requires that it persists for 30 minutes or longer. This means that a patient reporting pain freedom at 2 hours but reports pain again at 2.5 hours will not have an event time of 2 hours but will still be at risk of having an event. In these analyses, censoring with respect to first rescue medication use still applies. Note that the time between assessments is longer than 30 minutes after the 4-hour assessment but that the criterion of persisting pain freedom/absence of MBS/pain relief requires that the patient reports pain freedom/absence of MBS/pain relief at two successive timepoints.

12 Hours Cut-off

An analysis similar to the primary analysis will be conducted, where only data up to and including the 12-hour assessment will be used. Rules for censoring will be the same as those used for the primary analysis, except that a time value will be administratively censored at 12 hours instead of at 48 hours.

4 Hours Cut-off

An analysis similar to the primary analysis will be conducted, where only data up to and including the 4-hour assessment will be used. Rules for censoring will be the same as those used for the primary analysis, except that a time value will be administratively censored at 4 hours instead of at 48 hours.

4.3.6. Subgroup Analyses for Primary Endpoint

Summaries with descriptive statistics and frequency counts on the co-primary endpoints for both dose groups will be provided for the subgroups indicated below. Forest plots will also be created for subgroup analyses and will display number of patients, treatment differences, SEs, and p-values. The subgroups will be:

- Concomitant migraine preventative treatment (use any vs. no use)
- Concomitant migraine preventative treatment (use anti-CGRP vs. use others vs. no use)
- Sex (female vs. male)
- Race (black or African American vs. white vs. other)
- Age Group (< 65 years vs. ≥ 65 years)
- Region (North America vs. Rest of World)
- Duration of migraine history at baseline (≤15 yrs, >15 yrs)
- Duration of migraine prior to the start of the infusion (< 2 hours vs. 2-4 hours vs. > 4 hours)

- Impact of COVID-19 outbreak (patients randomized before vs. on or after 19 March 2020, with cut-off date selected based on when the impact of COVID-19 was seen in both the USA and Georgia independently).

5. BASELINE, DISPOSITION, AND EXPOSURE

5.1. Study Day Analysis Window

Study day is defined as:

Study day = date of assessment - date of dosing

Analysis Windows used to report non-diary endpoints are outlined in Table 1.

Table 1 Analysis Windows

Visit	Range	Target Day	Observation used for analysis, if more than one exists
Screening	< Day 0		First value
Day 0	Day 0 to Day 7	Day 0	Closest to Target Day
Week 4	> Day 7	Day 28	Closest to Target Day

Note: If two observations exist with same distance to target day, use first observation.

5.2. Definition of Baseline

The baseline assessment will be the latest available valid measurement taken prior to the administration of investigational product.

5.3. Demographics and Baseline Characteristics

Subject demographic and baseline characteristic information listed as follows will be summarized descriptively for the safety population:

- Age (years)
- Age Group (< 65 years, 65 - 75 years)
- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Baseline Weight (kg), Height (cm), Baseline BMI (kg/m^2)
- Region (North America, Rest of World)
- Concomitant migraine preventative treatment (use, no use)

Demographics and baseline characteristics will also be presented subgrouped by randomization before vs. on or after 19 March 2020, based on the safety population.

In addition, subject listings displaying information about family history and substance use (only including patients that actually had substance use) will be produced.

5.3.1. Qualifying Migraine Assessment and baseline score

The duration of migraine prior to the start of the infusion, whether or not the patient experienced an aura during the qualifying migraine, and answers to the question "What, if anything, triggered this migraine" will be summarized in a table by treatment group.

Characteristics of the qualifying migraine for each subject will be listed.

Summaries of the migraine status immediately before infusion will also be provided by treatment group. This includes: severity of headache pain, MBS, and whether or not the patient had nausea, light sensitivity (photophobia), or sound sensitivity (phonophobia).

In order to assess the potential impact of the COVID-19 outbreak on the study population, migraine status will be presented subgrouped by randomization before vs. on or after 19 March 2020.

The summaries and listing will be based on the safety population.

5.4. Subject Disposition

The number of subjects randomized, treated, had an incomplete infusion, and terminated from the clinical trial early will be summarized. The reason for early discontinuation from the clinical trial will be summarized. Subjects randomized but not included in the full analysis population and the reasons for exclusion will be summarized. The number of subjects screened and summary of screen failure reasons will also be summarized. Additionally, the summary of subjects present at each visit will be summarized.

A listing of entry criteria that were not met will be produced.

The number of patients randomized and the number of patients withdrawn from the study, including reason for the withdrawal, before and after 19 March 2020, will be summarized in order to assess the impact of the COVID-19 outbreak.

In addition, the visits will be tabulated by type of visit (onsite or remotely) and treatment group based on the safety population, to assess the potential impact of the COVID-19 outbreak on the visit structure.

The number of subjects in each analysis population will be summarized.

5.5. Prior and Concomitant Medications

Each medication will be recorded as prior, concomitant, or both prior and concomitant:

- Prior only: Medications with a stop date before the treatment dosing date will be considered prior medications.
- Concomitant only: Medications with a start date on or after the treatment dosing date will be considered concomitant medications.
- Prior and Concomitant: Medications with a start date before the treatment dosing date and continued past treatment dosing date (with a stop date after the treatment dosing date, or ongoing) will be considered prior and concomitant medications.

A medication with an incomplete stop date will be considered concomitant if:

- Month is missing, and year is equal to or after the year of the infusion date, or
- Day is missing, and year is equal to the year of the infusion date and month is equal to or after the month of the infusion date.

A tabular summary of concomitant medications by drug class and generic name will be provided for the most frequently used concomitant medications (defined as being reported for 10% or more of eptinezumab subjects) for the safety population. A listing displaying all concomitant medications will be provided for the safety population. In the data listing, each medication will be recorded as prior, concomitant, or both prior and concomitant.

The headache medications recorded in the eDiary will not be integrated with the concomitant medications as these two data capture tools have distinctly different format, purpose and functionality. These diary-based results will be summarized in a separate output. For these, the percent of days that subjects used headache medication will be summarized by treatment group. The following type of medication in eDiary will be used for summary: Triptans, Nausea medication, Sleep medication, NSAIDs, Analgesics, Opioids, Medical device.

5.6. Medical History

Medical history will be coded using MedDRA version 20.1. Medical History will be tabulated for the safety population by system organ class, preferred terms and treatment group.

5.7. Migraine History

Migraine history including age at diagnosis, the average number of headache/migraine days per 28-day period in the 3 months prior to screening, whether the patient suffers from aura, migraine attacks' association to headache of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia, number of years that the patient has suffered from migraines as well as migraine symptoms (answer to "Migraines can be brought on by") will be summarized in a table by treatment group for the safety population.

5.8. Study Drug Exposure

Study drug exposure will be summarized for the safety population with descriptive statistics for the following variables by treatment groups:

- Number and percent of subjects who received treatment after randomization
- Number and percent of subjects with dose interruption
- Number and percent of subjects who were in the study for 0, 1, 2, 3, 4, and > 4 weeks after infusion as well as descriptive statistics for number of days spent in the study after infusion
- Exposure time (end of infusion time – initiation of infusion time)

A listing of subjects who had dose interrupted will be provided.

5.9. eDiary Compliance

Patients have scheduled eDiary assessments at the following 14 time points:
just before infusion, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, and 48 hours. The missing rate at each time point will be summarized descriptively based on the safety population.

6. ANALYSIS OF SAFETY ENDPOINTS

6.1. Adverse Events

Adverse events are collected from the time of informed consent through the final subject visit. A treatment-emergent adverse event (TEAE) is an adverse event with a start date and time on or after the date and time of the infusion. Only TEAEs will be included in summary tables.

Verbatim descriptions of adverse events will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and converted to the same version (version 20.1). All adverse events are assessed by the investigator using five severity grades. AEs are also determined by the investigator to be related or not related to study drug.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as specified below. No duration will be calculated for adverse events with incomplete start-or stop dates, or for ongoing adverse events.
Imputation rules:

- Missing onset day (where UK and UKN indicate unknown or missing day and month respectively) UK-MMM-YYYY:
    - If the month and year are different from the month and year of the infusion, assume 01-MMM-YYYY;

  - If the month and year are the same as the infusion month and year, and the end date (after any imputation) is on or after the infusion, then assume the date of the infusion;
  - If the month and year are the same as the infusion and the end date (after any imputation) is prior to the infusion, then assume the end date for the onset date.
- Missing onset month DD-UKN-YYYY/UK-UKN-YYYY:
  - If the year is different from the year of the infusion, assume 01-JAN-YYYY of the collected year;
  - If the year is the same as the infusion, and the end date (after any imputation) is on or after the infusion, then assume the date of the infusion;
  - If the year is the same as the infusion, and the end date (after any imputation) is prior to the infusion, then assume the end date for the onset date.
- Missing end dates:
  - UK-MMM-YYYY: assume the last day of the month;
  - DD-UKN-YYYY/UK-UKN-YYYY: assume DD-DEC-YYYY/31-DEC-YYYY.

Tables by preferred term (PT) and tables by system organ class (SOC) and preferred term will be sorted in descending order by the percentage of patients in the eptinezumab 100 mg treatment group.

For the safety population, the following tabular summaries will be created:

- An overall summary of TEAEs will present the number and percentage of subjects with at least 1 reported TEAE, study drug related TEAE, serious TEAE, study drug infusion interruption, and death
- TEAEs by SOC and preferred term
- TEAEs by SOC, preferred term, and maximum severity
- Study drug related TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs that led to study drug infusion interruption by SOC and preferred term
- TEAEs that led to early withdrawal from study
- Serious TEAEs by SOC and preferred term

For incidence reporting, if a subject reported more than 1 AE that was coded to the same preferred term/system organ class, the subject will be counted only once for that specific preferred term/system organ class. For TEAEs presented by severity, the worst severity for each event during the clinical trial will be presented for each subject. If the severity is

missing for a TEAE, then a severity of "Severe" (Grade 3) will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

For TEAEs presented by relationship to study drug, the closest relationship to study drug for each event during the clinical trial will be presented for each subject. If the relationship to investigational product is missing for a TEAE, a causality of "Related" will be assigned. The imputed values for relationship assessment will be used for incidence summaries, while the actual values will be presented in data listings.

All AEs, SAEs, TEAEs leading to study drug infusion interruption, SAEs leading to death and Grade 4 or higher AEs will be displayed in separate listings. In case of any deaths in the study, all adverse events for patients who died will be listed.

The listings will include Subject ID, actual treatment received, SOC, preferred term, investigator term, start and stop date of the AE, whether or not the AE was treatment emergent, duration, frequency (pattern), severity, relatedness, action taken, outcome, and seriousness of the AE. Imputed start or stop dates will not be displayed in listings of AEs.

6.1.1. Adverse events of special interest

Adverse events of special interest include the following.

Hypersensitivity and Anaphylactic Events

The subset of adverse events with a MedDRA coded SOC of Immune system disorders and PTs of Hypersensitivity, Anaphylactic reaction and Anaphylactoid reaction.

Events Associated with Suicide

The subset of adverse events with a MedDRA coded SOC of Psychiatric disorders and PTs of Depression suicidal, Intentional self-injury, Suicidal behavior, Suicidal ideation, Suicide attempt and Self injurious behavior.

Cardiovascular Events

The subset of adverse events with

- A MedDRA coded SOC of Cardiac disorders and PTs of Atrial fibrillation, Bradycardia, chest pressure, Palpitations, Sinus bradycardia, Sinus tachycardia and Tachycardia, or
- a MedDRA coded SOC of Investigations and PTs of Blood pressure increase, Blood pressure systolic increase, Elevated blood pressure, Heart rate increased, Heart rate decreased, Heart rate irregular, Electrocardiogram abnormal, Electrocardiogram Q wave abnormal, Electrocardiogram QT interval abnormal, and Electrocardiogram QT prolonged, or
- a MedDRA coded SOC of Nervous system disorders and PTs of Syncope, or

- a MedDRA coded SOC of Vascular disorders and PTs of Flushing, Hot flush, Hypertension, Hypotension, Ischemia, and Prehypertension, or
- a MedDRA coded SOC of General disorders and administration site conditions and PTs of Chest pain and Feeling hot.

Nervous System Events

The subset of adverse events with a MedDRA coded SOC of Nervous system disorders and PTs of Seizure.

Hepatic Events

A subset of adverse events with a MedDRA coded SOC of Investigations and PTs of Alanine minotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, and Transaminases increased.

Events Associated with Study Drug Infusion

A subset of adverse events withing one week of dosing with

- a MedDRA coded SOC of Skin and subcutaneous tissue disorders and PTs of Dermatitis bullous, Pruritus, Pruritus allergic, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash macularpapular, Rash papular, Rash pruritic, Swelling face, and Urticaria, or
- a MedDRA coded SOC of General disorders and administration site conditions and PTs of Infusion site discomfort, Infusion site eczema, Infusion site erythema, Infusion site extravasation, Infusion site nerve damage, Infusion site pain, Infusion site paresthesia, Infusion site pruritus, Infusion site rash, Infusion site reaction, Infusion site swelling, and Injection site paraesthesia, or
- a MedDRA coded SOC of Gastrointestinal disorders and PTs of Lip oedema, Oral pruritus, and Paraesthesia oral, or
- a MedDRA coded SOC of Respiratory, thoracic and mediastinal disorders and PTs of Choking sensation, Cough, Dyspnoea, Nasal congestion, Oropharyngeal pain, Rhinitis allergic, Rhinorrhoea, Sinus congestion, Sneezing, Throat irritation, and Wheezing.

Adverse Events of Interest Analysis

The adverse events of special interest (AESI) will be summarized and listed in the following categories:

- AESIs by system organ class and preferred term.
- AESIs by system organ class, preferred term, and maximum severity

- AESIs by system organ class, preferred term, and relationship to study drug.
- AESIs that lead to infusion interruption by system organ and preferred term
- AESIs with action taken of study drug discontinuation by system organ class and preferred term
- AESIs assessed as serious by system organ class and preferred term

6.2. Clinical Laboratory Evaluations

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

The potentially clinically significant (PCS) criteria used for the clinical safety laboratory tests are the Lundbeck standard PCS criteria described in *SOP_09978: PV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 4.

Descriptive statistics for the laboratory parameters, both absolute values and changes from baseline, will be presented by test and scheduled visit and the last assessment. All available post baseline assessments will be included in the identification of the last assessment.

Low, normal, and high classifications will be applied to determine whether the laboratory test value was below (low), within (normal), or above (high) the reference range for that test. The number and percentage of subjects with shifts in their results from classification of baseline (low, normal, high) to classification of the minimum/maximum post-baseline (low, normal, high) will be presented.

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

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

All the adverse events in patients with post-baseline PCS values will be listed by treatment group and patient ID; the listings will include all available values for the variable with flagging of PCS values and out-of-reference-range values, 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.

Due to the COVID-19 outbreak, local laboratories rather than the planned centralized laboratory have been used at some sites in Georgia. Data from the local laboratories will

be included in the ADaM datasets, but only normal ranges from the laboratory and PCS range classifications will be used in the analyses. Thus, the absolute values and the change from baseline values from local laboratories will be excluded from summary statistics, but included in any listings, if relevant.

If a visit was performed remotely, study procedures such as collection of blood samples for laboratory analyses, unscheduled visits may have been performed with extended visit window up to three weeks after the planned Week 4 visit. In such cases, the statistical analysis of Week 4 values will include the unscheduled visit.

6.2.1. Potential Drug-induced Liver Injury (DILI)

Liver function test data will also be provided in separate listings for:

- Subjects who possibly met Hy's Law criteria (ie, had any elevated ALT or AST of >3xULN, and increase in total bilirubin >=2xULN, and ALP <2xULN at the same visit)
- Subjects who met any one or more of the following criteria at any post-baseline visit (list laboratory parameters ALT, AST, ALP and total bilirubin only)
    - Either ALT or AST or both >2x, >3x, >5x, >10x, or >20xULN
    - ALP >1.5xULN
    - Total bilirubin >2xULN
- Subjects who had any elevated ALT or AST of >3xULN, and an increase in total bilirubin >1.5xULN at the same visit

A summary table will also be provided for number of subjects who met any of the criteria specified above at any post-baseline visit.

Data from local laboratories will be included in the DILI classification.

6.3. Vital Signs

The PCS criteria used for vital signs are the Lundbeck standard PCS criteria described in *SOP_09978: PV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 5.

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

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

All the adverse events in patients with post-baseline PCS values will be listed by treatment group and patient ID; the listings will include all available values for the variable with flagging of PCS values and out-of-reference-range values, 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.

The observed data at baseline and change from baseline for each measurement day and last assessment will be summarized for each parameter with descriptive statistics. All

available post baseline assessments will be included in the identification of the last assessment.

6.4. Electrocardiogram Results

Results for each ECG parameter will be summarized by treatment group at each visit and last assessment for the observed data and for changes from baseline. All available post baseline assessments will be included in the identification of the last assessment.

The overall ECG assessment as determined by the investigator will be reported as "Normal" or "Abnormal – not clinically significant", or "Abnormal – clinically significant" and summarized by visit and across visits. A shift table of overall ECG assessment from baseline to the most extreme post-baseline value will be presented.

Additionally, the highest post-baseline value for QTc interval (using Fridericia's correction) will be summarized descriptively as a categorical variable. Each QTcF value for a given subject will be grouped into 3 categories:

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

The largest post-baseline change in QTcF measures will also be analyzed as categorical variables. The change in QTcF in a given subject will be grouped into 2 categories:

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

Relevant ECG data will also be displayed in separate listings for:

- Subjects who shifted from normal or abnormal not clinically significant at baseline to abnormal clinically significant during the treatment period
- Subjects who had an abnormal clinically significant assessment at any time during the study
- Subjects who ever had a QTcF interval increase from baseline > 30 msec during the treatment period
- Subjects who ever had any value of QTcF interval >= 450 msec at any visit

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

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

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

All the adverse events in patients with post-baseline PCS values will be listed by treatment group and patient ID; the listings will include all available values for the variable with flagging of PCS values and out-of-reference-range values, 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.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a patient questionnaire that evaluates suicidal ideation and behaviors. In this study, the C-SSRS is assessed at screening using the “Baseline/Screening Version” and at subsequent timepoints using the “Since Last Visit” version. The screening assessment will assess suicidal ideation during the past 6 months and suicidal behaviour during the past 5 years. The results (yes/no) from the 5 questions under suicidal ideation and the 5 questions under suicidal behavior will be summarized at screening (using the answers to the Baseline/Screening version) and post baseline using percentages and counts. The denominator for percentages will be the number of subjects with a C-SSRS assessment in the relevant period that is, for the screening assessments it will equal the number of patients with a C-SSRS assessment at screening, and for post-baseline assessments it will equal the number of patients with a C-SSRS assessment at any time post baseline. The summaries will also include answers to “Has the subject engaged in Non-Suicidal Self-Injurious Behaviour?”. The post-baseline by-question summary will list a subject as "yes" if they selected yes at any time after baseline.

For patients with any post-baseline suicidal behavior, if any, listings will be prepared including all C-SSRS scores for these patients.

6.6. Pregnancies

Any reported positive pregnancy results or reported pregnancies will be listed.

6.7. Other

Emergency room visits and procedures will be listed for any patients with an emergency room visit due to migraine during the study.

7. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

The use of the logrank test for assessing the effect of treatment with eptinezumab has been removed. In order to account for the stratification, the effect of treatment will be assessed using the likelihood ratio test from the stratified Cox model, which is also used for estimating the treatment effect.

In the study protocol an exploratory endpoint denoted “Pain relapse when the subject was headache pain-free at 2 hours” is included. However, it is expected that the analyses of sustained pain freedom through 24 and 48 hours endpoints will provide sufficient insight into this matter, and therefore no analysis of the specific pain relapse endpoint will be included.

An analysis of time to rescue medication use has been added as an exploratory analysis and will be analysed using the same methodogy as for the co-primary endpoints.

A number of sensitivity analyses has been added.

The secondary endpoints have been redefined due to comments made by the FDA to the previous version of the SAP. The testing strategy for secondary endpoints has been changed from an alpha-sharing strategy to a hierarchical strategy.

Analyses have been added in order to assess the potential impact of the COVID-19 outbreak.

8. APPENDIX I

Table 2 Schedule of Events and Assessments

Assessment	Screening Period (Day -56 to Day -1)		Rand/ Dosing Day	End of Study/Early Term (Day 28 ± 3)
	Screening Visit	Weekly Contact [7]	Day 0 Visit	Week 4 Visit
Informed Consent	X			
Inclusion/Exclusion Criteria[1]	X		X	
Demographics	X			
Medical History (including family and social history)	X			
Height, Weight and BMI[2]	X		X	X
Physical Exam	X			X
Vital Signs[3]	X		X	X
eDiary Training[1]	X		X	
eDiary Completion[4]			X	
Migraine History	X			
Qualifying Migraine Assessment[1]			X	
HIT-6	X			X
mTOQ-6	X			X
PGIC				X
C-SSRS[5]	X	X		X
12-lead ECG	X			X
Hematology/Chemistry[1]	X		X	X
Serology (HIV/Hepatitis B and C)	X			
Urine Drug Screen[1]	X		X	
Urine Pregnancy (hCG) Test[1]	X		X	X
AE Review[1,6]	X	X	X	X
Concomitant Medication Review[1,6]	X	X	X	X
Randomization[1]			X	

Eptinezumab/placebo administration			X	

[1] Prior to dosing on Dosing Day
[2]Height and BMI only collected at Screening visit. Weight collected at Screening, Day 0 and Week 4 visits.
[3] On Day 0, vital signs should be collected pre-dose and any time prior to the subject leaving the site post-dose.
[4] An electronic diary (eDiary) will be assigned before dosing on the Day 0 visit to collect migraine data pre-dose through 48 hours. Additionally, subjects will complete eDiary data entry from Day 3 until a new migraine is reported.
[5] C-SSRS "Baseline/Screening Version" should be used at the screening visit and C-SSRS "Since Last Visit Version" should be used at all subsequent timepoints. Complete C-SSRS at Screening, Week 4 and, if applicable, the weekly contact after the subject has been in screening for 4 weeks. If the screening period exceeds 28 days, the C-SSRS "Since Last Visit Version" should be completed via a phone call to the subject on Screening Day 29 (+7 days).
[6] If the screening period exceeds 28 days, AEs and concomitant medications should be reviewed via a phone call to the subject on Screening Day 29 (+7 days).
[7] Weekly contact attempts will occur in which updates are obtained from the subject via a mobile application or a phone call from the site staff to check in with the subject during the screening period.

Table 3 Schedule of Events and Assessments for Day 0 through 48 Hours

Assessment	Pre-dose	Dose		Post Start of Infusion												
			Start of Infusion	0.5 hr (+20 min)	1 hr (+20 min)	1.5 hr (+20 min)	2 hr (+20 mins	2.5 hr (+20 min)	3 hr (+20 min)	3.5 hr (+20 mins)	4 hr (+2 hr)	6 hr (+3 hr)	9 hr (+3 hr)	12 hr (+12 hr)	24 hr (+12 hr)	48 hr (+12 hr)
Inclusion/Exclusion Criteria	X															
eDiary Training	X															
eDiary Completion[1]	X		X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Qualifying Migraine Assessment	X															
Vital Signs[2]	X										X					
Hematology/Chemistry	X															
Urine Drug Screen	X															
Urine Pregnancy (hCG) Test	X															
Adverse Event Review	X															
Concomitant Medication Review	X															
Randomization	X															
Eptinezumab/placebo administration		X														

[1] An electronic diary (eDiary) will be assigned before dosing on the Day 0 visit to collect migraine data. eDiary will be completed by the subject. While the subject is in the clinic the study staff will provide close oversight to ensure subject completes eDiary at all timepoints, as close to the beginning of the window as possible.
[2] On Day 0, vital signs should be collected pre-dose and any time prior to the subject leaving the site post-dose.
[3] Immediately when the infusion is started, the subject will be required to press a button on the eDiary device to indicate that the infusion has started.

Note: Timepoint windows only pertain to subject completion of eDiary.

9. APPENDIX II

9.1. SAS® Code

The SAS® code displayed below performs the analyses described in sections 4.3.1 and 4.3.2 for analyzing the co-primary and key secondary endpoints.

For the time-to-event endpoints, it is assumed that a dataset containing one record per patient is available. TIME represents the time from start of infusion to the endpoint (e.g. time to headache pain freedom), STATUS represents whether or not an event was observed i.e. in the case of headache pain freedom, STATUS = 1 indicates that headache pain freedom was acheived at the timepoint given by TIME and STATUS = 0 indicates that headache pain freedom was not acheived (censored observation). REGION represents the regional stratification factor (North America vs. Rest of World), CONMED represents the stratification factor for concomitant preventive treatment (use vs. no use), and TREAT represents the treatment received in the study.

For the binary endpoints the treatment and stratification variables are the same as described above. For these analyses, RESPONDER represents whether or not the endpoint was achieved for the patient – for instance when considering 2-hour headache pain freedom, RESPONDER = "Y" indicates that the patient experienced headache pain freedom at the 2-hour timepoint with the absence of rescue medication and RESPONDER = "N" indicates that the patient did not experience headache pain freedom at the 2-hour timepoint.

9.1.1. Cox proportional hazards model

The stratified Cox proportional hazards model with Efron's method of tie handling with a single treatment covariate will be fitted using the following code. The values for obtaining median estimates for each treatment group are saved in the dataset "survdat". From "survdat" the values can be averaged across strata with weights according to the description in section 4.3.1 to obtain median estimates for each treatment group:

```
proc phreg data = xxx;
    class TREAT (ref = 'PBO');
    strata REGION CONMED;
    model TIME * STATUS(0) = TREAT / ties = EFRON;
    hazardratio TREAT / cl = pl;
    baseline out = survdat survival = survival / group = TREAT diradj;
run;
```

9.1.2. Cochran-Mantel-Haenszel test

The Cochran-Mantel-Haenszel test adjusting for the study's stratification factors and computation of the odds ratio, as well as the computation of difference in rates and associated Wald confidence intervals not taking the stratification into account, will be performed using the code given below. For stratified 2x2 tables all three of the CMH statistics test the same hypothesis.

```
proc freq data = xxx;
   tables REGION*CONMED*TREAT*RESPONDER / cmh;
   tables TREAT*RESPONDER / riskdiff (CL=(WALD));
run;
```

10. APPENDIX III

Table 4 PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
Haematology / Coagulation				
B-haemoglobin	HGB	g/dL	≤ 9.5 (women)	≥ 16.5 (women)
			≤ 11.5 (men)	≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women)	≥ 6.0 (women)
			≤ 3.8 (men)	≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women)	≥ 0.50 (women)
			≤ 0.37 (men)	≥ 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	IU/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	IU/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	IU/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	IU/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)

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
				≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0
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	%		≥ 6.5
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	
Cardiac/Skeletal/Muscle				
S-creatine kinase (total)	CK	IU/L		≥ 400 (women) ≥ 750 (men)

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

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

Table 5 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 6 PCS Criteria for ECG Parameters

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

Increase/decrease is relative to the baseline value.

11. REFERENCES

1. ICH. ICH Harmonised Guideline E9 (R1): Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. November 2019.