Clinical Study Protocol

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

Eptinezumab

Study No.:	19386A (Alleviate)
EudraCT/IND No.:	2020-001969-37 / 151358
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 19386A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Eptinezumab
Study Title Interventional, randomized, double-blind, parallel-group, placebo-controlled delayed-start study to evaluate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache (eCH)	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • To evaluate the efficacy of eptinezumab in patients with eCH	**Primary endpoint:** • Change from Baseline in the number of weekly attacks (Weeks 1–2) **Key secondary endpoints:** • Response: ≥50% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2) • Change from Baseline in the number of daily attacks (Days 1-3) • Change from Baseline in the number of weekly days with < 3 attacks per day (Weeks 1-2) • Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks) • Number of attacks starting <= 24 hours after the start of the first infusion of IMP

Primary Objective (continued) • To evaluate the efficacy of eptinezumab in patients with eCH	**Secondary endpoints:** • Change from Baseline in the daily mean score on 5-point self-rating pain severity scale (Days 1- 3) • Change from Baseline in the number of weekly attacks (Week 1) • Change from Baseline in the number of weekly attacks (Week 2) • Response: ≥50% reduction from Baseline in the number of weekly attacks (Week 1) • Response: ≥30% reduction from Baseline in the number of weekly attacks (Week 1) • Response: ≥30% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 1) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the number of weekly attacks (Weeks 1-4) • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-4) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the mean score on 5-point self-rating pain severity scale (average per attack over a week) for each of Weeks 1, 2, 3, and 4 • Change from Baseline in the number of weekly attacks for each of Weeks 3 and 4 • Patient Global Impression of Change (PGIC) score at each of Weeks 1, 2, and 4 • Change from Baseline in the Sleep Impact Scale (SIS) domain scores at each of Weeks 2 and 4
	Exploratory endpoints: • Response: 75% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-4) • Time from first infusion of eptinezumab to resolution of cluster headache bout (within the first 16 weeks; only for patients randomized to eptinezumab at Baseline) • Use (yes/no) of abortive medication (triptans or O2) for each of Weeks 5 to16

	• Use (yes/no) of preventive medication for each of Weeks 1 to 16 • Use (yes/no) of transitional treatment for each of Weeks 5 to 16 • Number of attacks starting <= 24 hours after the start of the first infusion of IMP divided into three parts: one for attacks starting > 0 and <= 8 hours after the start of the first infusion of IMP, one for attacks starting >8 and <=16 hours after the start of the first infusion of IMP, and one for attacks starting >16 and <=24 hours after the start of the first infusion of IMP • Change from Baseline in the EQ-5D-5L Visual Analogue Scale (VAS) score at Weeks 8 and 16 • Patient Global Impression of Change (PGIC) score at Weeks 8 and 16 • Number of weekly attacks for each of Weeks 5 to 16 • Severity of pain (average per attack over a week) based on a 5-point self-rating pain severity scale for each of Weeks 5 to 16
Estimands to Address the Primary Objective	
Estimand for the primary endpoint: The primary estimand will be the mean difference in change from Baseline in the number of weekly attacks (Weeks 1-2) between patients with episodic cluster headache treated with eptinezumab and placebo, without use of transitional treatment, and regardless of use of abortive or preventive medication, and infusion interruption or termination before full dose is received.	
Secondary Objectives • To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity	**Secondary endpoints:** • Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) at Weeks 2 and 4 • Health Care Resources Utilization (HCRU) at Baseline and Week 4 • Change from Baseline in the Work Productivity Activity Questionnaire: General Health second version (WPAI:GH2.0) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Week 4
Safety Objectives • To evaluate the 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

Study Methodology

- This is an interventional, multi-regional, randomized, double-blind, placebo-controlled delayed-start study, designed to demonstrate the efficacy and safety of eptinezumab in patients with episodic Cluster Headache (eCH).
- The target population for this study is defined as patients with eCH, based on the IHS ICHD-3 classification, with an adequately documented record or reliable history of eCH prior to Screening Visit 1 and confirmed via prospectively collected information in the eDiary during Screening Period 2. The study is planned as a global study.
- 304 patients will be randomly allocated via a randomization system to one of the two initial treatments: eptinezumab 400 mg, or placebo, in a ratio of 1:1.
- The total study duration from Screening Visit 1 to the Safety Follow-up Visit is approximately 77 weeks and includes Screening Period 1 (approximately 12 months / 52 weeks), Screening Period 2 (7 days), a Placebo-controlled Period (4 weeks), an Active Treatment Period (4 weeks), a Post-treatment Observational Period (8 weeks), and a Safety Follow-up Period (8 weeks).
- The patients can be screened up to 12 months prior to Screening Period 2.
- The patients will enter Screening Period 2 as soon as possible after they experience the beginning of a cluster headache bout, which is characterized by the presence of at least one typical cluster headache attack, and not later than 1 week after the start of the first attack. Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enroll this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient.
- Repeat of Screening Visit 1 and Screening Visit 2 will be allowed for patients who do not meet pre-defined specific eligibility criteria (details are presented in the study protocol).
- Eligible patients will be randomly assigned to receive at the Baseline Visit (Day 0/Visit 3) either eptinezumab 400 mg or placebo, administered as an IV infusion over 45 minutes (+15 minutes). Preferably the infusion should be administered in the morning.
- All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (eptinezumab 400 mg or placebo), administered over 45 minutes (+15 minutes), at the end of Week 4 (Visit 6) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patients randomized to placebo will receive eptinezumab 400 mg.
- The Safety Follow-up Visit will take place at Week 24 (Visit 10), 20 weeks (5 half-lives) after the second IMP administration.
- Patients who withdraw from the study, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-Up Visit (SFU), scheduled 20 weeks after the last IMP administration.
- Eligibility will be assessed during Screening Period 1, during Screening Period 2, as well as before the administration of IMP at the Baseline Visit (Day 0/Visit 3).
- Study visits:
  - The following visits will be site visits: Screening Visit 1, Screening Visit 2, Baseline Visit (First Visit of the Placebo-controlled Period (Day 0/Visit 3) (randomization and IMP infusion)), Last Visit of the Placebo-controlled Period at the end of Week 4 (Visit 6 - second IMP infusion), Completion Visit at Week 16 (Visit 9) and SFU visit at Week 24 (Visit 10) or Withdrawal Visit, if applicable.
  - All other study visits will be phone contact visits.
- In exceptional situations, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, site visits may only consist of blood sampling and urine sampling (for clinical laboratory tests, exploratory eptinezumab quantification, ADA including Nab, and exploratory biomarkers), and ECG, vital signs, physical and neurological examinations, adverse event recording, and IMP administration, while the remaining assessments (eDiary, ePROs, C-SSRS, and investigator evaluations) can be conducted remotely via a virtual clinic visit. These cases must be approved by the CRO's Medical Monitor.
- Patients will be assigned an eDiary at the Screening Visit 2 and will be required to complete this daily from the time of Screening Visit 2 until the Completion Visit (Week 16/Visit 9) or until the Withdrawal Visit.

- During the study visits with IMP infusion, safety assessments will be performed before and after the infusion. At these visits, AEs as well as safety laboratory tests, ECG, weight, and vital signs, including body temperature, will be collected. Electronic patient-reported outcomes (ePROs) must be completed prior to infusion.
- An interim futility analysis that is unblinded to a study independent team, evaluating efficacy, will be performed based on 204 randomized and treated patients who have had the chance of completing the Visit 6 (Week 4). Randomized patients with an infusion on the same date, but after 204 patients have been treated, will also be included in the cut-off. Recruitment continues while the interim analysis is conducted. Based on the interim analysis result of the primary endpoint, a decision will be made to either continue the recruitment, or to end enrolment (see Interim Analysis below). Details of information flow and the interim process will be described in a separate interim analysis charter.
- Blood samples for IMP quantification will be collected at regular intervals during the study (see Panel 2) and will be reported separately.
- The study design is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarized in Panel 2.

Number of Patients Planned

304 patients recruited from specialist settings are planned for randomization: 152 patients in the eptinezumab 400 mg group and 152 patients in the placebo group.

Target Patient Population

Main Inclusion Criteria

The patient has episodic cluster headache, as defined by IHS ICHD-3 classification, with an adequately documented record or reliable history of eCH of at least 12 months prior to Screening Visit 1.

The patient has a prior history of cluster period(s) lasting 6 weeks or longer, when untreated.

The patient is able to distinguish cluster headache attacks from other headaches (i.e. tension-type headaches, migraine).

The patient is, at Screening Visit 2, in cluster headache bout, characterized by the presence of at least one typical cluster headache attack, that started not later than 1 week prior to Screening Visit 2. In the opinion of the investigator the cluster headache bout is likely to continue for at least another 6 weeks based on prior cluster period history. Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enroll this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient.

The patient has during Screening Period 2 based on prospectively collected information in the eDiary a weekly cluster headache attack frequency of a (*this requirement should not be shared with the patient*):

a. minimum of at least 7 total cluster headache attacks out of the 7-day Screening Period 2
b. maximum of 56 cluster headache attacks out of the 7-day Screening Period 2

The patient has an adequately documented record or reliable history of previous acute and preventive medication use for eCH, for at least 12 months prior to Screening Visit 1.

The patient has demonstrated compliance with the eDiary by entry of data for at least 6 of the 7 days of Screening Period 2.

The patient has a medical history of first symptoms of cluster headache from ≤60 years of age.

The patient is aged ≥18 and ≤75 years at Screening Visit 1.

Main Exclusion Criteria

The patient has experienced failure on a previous treatment targeting the calcitonin gene-related peptide (CGRP) pathway (anti-CGRP mAbs and gepants).

The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, complex regional pain syndrome).

The patient has a history or diagnosis of hypnic headache, hemicrania continua, new daily persistent headache, chronic migraine or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura and migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).

Patients with a lifetime history of psychosis, bipolar mania, or dementia are excluded. Patients with other psychiatric conditions whose symptoms are not controlled or who have not been adequately treated for a minimum of 6 months prior to Screening Visit 2 are also excluded.

The patient is, at Screening Visit 2, at significant risk of suicide (either in the opinion of the investigator or defined, using the C-SSRS, as the patient answering: "yes" to suicidal ideation questions 4 or 5 or answering: "yes" to suicidal behaviour within the past month). Patients who do not meet this criterion, but who are considered by the investigator to be at significant risk for suicide, are excluded.

The patient has a history of clinically significant cardiovascular disease, including uncontrolled hypertension, ischaemia or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).

The following recent and concomitant medications are disallowed or allowed with restrictions with respect to their use prior to or during the study (the list is not comprehensive):

a. Anti-CGRP therapies are disallowed for ≤5 half-lives for mAbs and ≤ 1 month for gepants prior to Screening Visit 2
b. Disallowed for 4 months prior to Screening Period 2 until the Safety Follow-Up Visit: botulinum toxin type A or B, that is administered in the head or neck area for treatment of cluster headache or other disorders, or for cosmetic use.
c. Disallowed for 2 months prior to Screening Period 1 until the Safety Follow-Up Visit: Psilocybin (mushrooms), LSD, or 2-bromo-LSD, or other illegal drugs
d. Disallowed for 30 days prior to Screening Period 2 and until the end of Week 4: Greater occipital nerve (GON) block, injected and oral corticosteroids
e. Disallowed for 30 days prior to Screening Period 2 until the Safety Follow-Up Visit:
    i. indomethacin
    ii. any other cranial or extracranial nerve block;
    iii. any neuromodulation treatment.
    iv. Gamma knife or other invasive procedures
f. Disallowed for 14 days prior to Screening Period 2 until the Safety Follow-Up Visit: methergine
g. Stable dose (with restrictions on the maximum dose) for one month prior to Screening visit 2 and until the end of Week 4: verapamil, topiramate, gabapentin, valproate, candesartan and lithium. Melatonin is allowed at any time with a maximum dose 9mg/day
h. Abortive therapies for cluster headache attack allowed: high-flow oxygen; oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen, NSAIDs, dihydroergotamine or ergot derivatives, octreotide
i. Allowed with restrictions: opioids, cannabinoids.

Investigational Medicinal Product, Dose and Mode of Administration

- Eptinezumab – 400 mg, Concentrate for Solution for Infusion 100 mg/ml added to 100 mL of 0.9% normal saline, intravenously
- Placebo – 100 mL of 0.9% normal saline, intravenously

The IMP will be administered at Day 0 and at the end of Week 4, by intravenous infusion over 45 minutes (+15 minutes)

Assessment Details/Biomarker Methodology
Pharmacodynamic/Exploratory Biomarker Assessments

- Blood sampling for exploratory plasma biomarker analyses (to be reported separately).

The assessments are summarized in Panel 2. Details for selected assessments are provided below.

Assessment Details

The assessments are summarized in Panel 2. Details for selected assessments which are non-standard/require more explanation/description are provided below. All scales used to assess efficacy and pharmacoeconomic information in this study, are patient-reported instruments.

eDiary

Patients will complete a daily cluster headache eDiary from Screening Visit 2 until the Completion Visit (End of Week 16)/Withdrawal Visit consisting of applications and reports which will be used to derive the cluster headache endpoints and medication use. The eDiary will be distributed to each patient at Screening Visit 2 after patient training on eDiary use by site staff. The eDiary data from the 7-day Screening Period 2 will be used to determine eligibility criteria, baseline cluster headache characteristics and eDiary compliance. Ongoing evaluation of eDiary compliance will be performed by the study site based on eDiary reports.

Sleep Impact Scale (SIS)

The SIS is a patient-reported scale to assess quality of life resulting from sleep disturbance. The SIS domains cover sleep impact on daily activities, emotional well-being, emotional impact, energy/fatigue, social well-being, mental fatigue, and satisfaction with sleep. Each item is rated on a scale ranging from 1 (always) to 5 (never). A higher score indicates better quality of life. It takes approximately 10 minutes to complete the questionnaire.

Health Care Resource Utilization (HCRU)

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

Statistical Methodology

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

- *all-patients-randomized set* (APRS) - all randomized patients
- *all-patients-treated set* (APTS) - all patients in the APRS who received infusion with double-blind IMP
- *all-patients-treated at interim set* (APTS_IN) – all patients in the APRS who were among the first 204 that received infusion with double-blind IMP. Patients in the APTS that were infused on the same date, but after the first 204 will also be included.

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

Baseline number of weekly attacks is derived from eDiary data collected in the Screening period 2 (day -7 to Day -1).

Unless otherwise specified, all testing will be done two-sided, based on a 5% significance level.

- Primary analysis of the primary endpoint:

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

  The strategy for imputation of missing data is given below and in details in the SAP:

  Weekly scores are calculated using pro-rating, when data has been observed for at least 4 out of 7 days, with the weekly score = the average daily score x 7.

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

  The pMI will generate 200 simulated data sets with complete assessment of number of weekly attacks for Weeks 1, 2, 3, and 4. Each of these 200 data sets will be analysed using the following MMRM model:

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

  The 200 results will be weighted together using Rubin's rule to obtain a pMI estimate, confidence interval, and p-value.

  Details are provided in the SAP.

- Analysis of the key secondary endpoints:

– The continuous key secondary endpoints (change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2), and change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)) will be analysed using the MMRM model presented in the section on primary analysis using the baseline value of the variable as baseline.

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

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

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

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

- Sensitivity analyses of the primary endpoint:

  The impact of missing data in the derivation of the number of weekly attacks averaged across Weeks 1-2 and the impact of the use of transitional treatment will be evaluated by applying different methods of imputation. Details will be described in the SAP.

- Interim analysis:

– An interim futility analysis will be performed based on 204 randomized and treated patients who have had the chance of completing the Week 4/Visit 6, to allow for stopping the study for futility if the level of efficacy is considerably lower than expected. If the estimated treatment effect for the primary endpoint is less than 1/3 of the expected effect size (3.00/3 = 1). Lundbeck may decide to stop the study for futility. The interim analysis will be performed by an independent CRO.
– The independent CRO will inform a predefined group of Lundbeck employees whether the criterion for the interim futility have been met or not. No further details of the interim analysis results will be provided.
– Details of the interim process will be described in a separate *Interim Analysis Charter*
– Details of the statistical analysis for the interim analysis will be described in an *Interim Statistical Analysis Plan*

Testing Strategy

Primary endpoint

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

Key secondary endpoints

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

A two-sided significance level of 0.05 will be used for the formal testing strategy.

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

Step 1

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

Step 2

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

Step 3

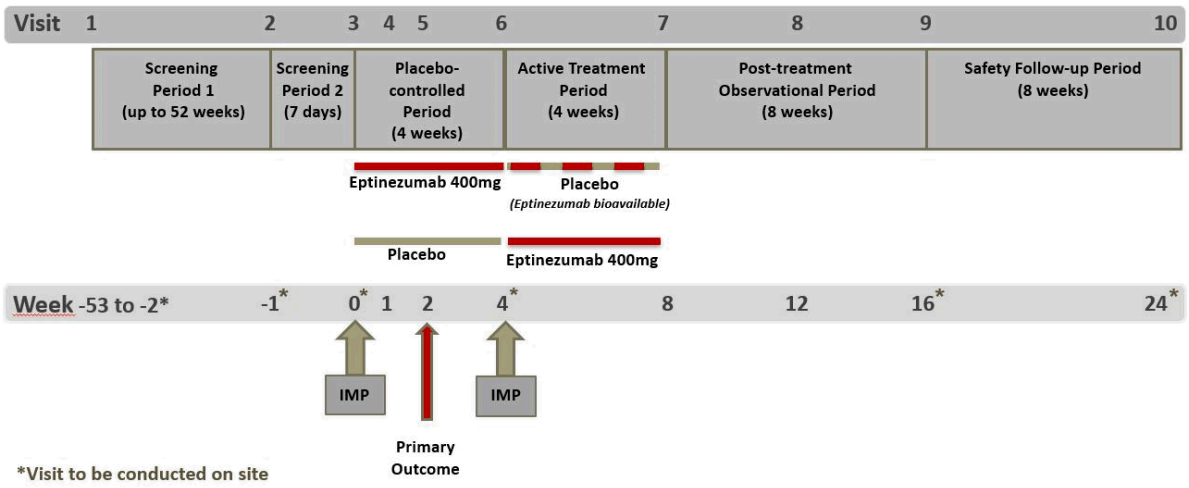
The steps for testing the key secondary endpoints in the order stated in the beginning of this section continues until a p-value >= 0.05 is encountered or all 6 key secondary endpoints are found to be statistically significant.

Sample Size Considerations

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

Assuming a difference of eptinezumab to placebo of -3.0 attacks with an SD = 9.0, 144 patients per treatment will provide 80% power for seeing an effect using a two-sided 5.0% significance level. Since the estimated treatment difference may be slightly decreased due to the use of pMI, an additional 5% of patients have been added. This yields a total of 152 patient per treatment.

Panel 1 Study Design



The study consists of Screening Period 1 (up to 52 weeks), Screening Period 2 (7 days), a Placebo-controlled Period (4 weeks), an Active Treatment Period (4 weeks), a Post-treatment Observational Period (8 weeks) and a Safety Follow-up Period (8 weeks). After randomisation, IMP (eptinezumab 400 mg or placebo) is administered by intravenous infusion at Baseline (Day 0/Visit 3) and primary outcome is collected at Week 2. At the end of Week 4, all patients will receive a second IMP infusion (placebo or eptinezumab 400 mg) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patients randomized to placebo will receive eptinezumab 400 mg. For all subjects, who complete the study, a Safety Follow-up Visit will be conducted 20 weeks after the last infusion of IMP, that is at Week 24. For subjects who withdraw from the study, the Safety Follow-up Visit will be conducted 20 weeks after their last IMP infusion.

Panel 2 Study Procedures and Assessments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

v Biobank may be excluded or optional per local regulation.

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

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

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

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

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

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

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

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

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

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

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

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRS	all-patients-randomized set
APTS	all-patients-treated set
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BSC	best supportive care
CGRP	calcitonin gene-related peptide
CH	Cluster Headache
CI	confidence interval
Cmax	maximum observed concentration
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	clinical research organization
CSR	clinical study report
DNA	deoxyribonucleic acid
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EC	ethics committee
ECG	electrocardiogram
eCH	episodic Cluster Headache
eCRF	electronic case report form
ePRO	electronic patient-reported outcome
EQ-5D-5L	Euroqol 5 Dimensions
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	Food and Drug Administration
GON	greater occipital nerve
hCG	human chorionic gonadotropin
HCRU	health care resource utilization
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	investigational medicinal product

IND	Investigational New Drug Application
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous
Lu	Lundbeck
mAbs	monoclonal antibodies
NAb	neutralizing antibody
NOAEL	no-observed-adverse-effect level
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PR	specific ECG interval describing atrioventricular conduction
QP	qualified person
QRS	specific ECG interval describing ventricular depolarization
QT	specific ECG interval describing ventricular depolarization/repolarization
QTc	heart-rate corrected QT interval
QTcF	heart-rate corrected QT interval using Fridericia's correction formula
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SFU	Safety Follow-Up
SNP	single-nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent elimination half-life
TEAE	treatment-emergent adverse event
TMF	trial master file
WPAI:GH2.0	Work Productivity and Activity Impairment, General Health second version

Major Changes Since Last Edition

No major changes have been made since the last edition of this CSP.

1 Introduction

1.1 Background

1.1.1 Overview

Episodic cluster headache is a rare but disabling primary headache disorder characterized by episodic attacks of intense unilateral headache, frequently associated with autonomic symptoms such as lacrimation, conjunctival injection, and nasal congestion (IHS ICHD-3).[1] The diagnosis of cluster headache (CH) is distinctly recognized and defined by the ICHD-3. The natural course of illness of episodic cluster headache can be conceptualized as consisting of two phases: (1) cluster periods (typically lasting weeks or months) composed of a series of 15-180 minute attacks of severe (often excruciating) unilateral headache pain attacks and cranial autonomic symptoms occurring near-daily to multiple times daily during the cluster period, and (2) attack-free remission periods that may last for weeks, months, or even years.

The social impact of cluster headache is considerable[2] and it is associated with substantial direct and indirect economic consequences.[3] Cluster headache has a prevalence of 0.1% with a 2-6 times higher average incidence rate for males compared to females.[4] However, the ratio might be lower due to misdiagnosis of cluster headache in females compared to males.[5] The life-time prevalence of cluster headache, based on a meta-analysis, showed a mean prevalence of 124 per 100,000, where episodic form was six times more prevalent than the chronic form that unlike the episodic form has no remission period, or the remissions lasts <3 months.[1,4]

There are significant unmet needs for just about every clinical aspect of the patient with cluster headache, particularly related to the severity of the disease and treatment options. Most patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable (using a Visual Analog Scale).[6]

The currently available preventive pharmacological treatments are unspecific, insufficient, and hampered by side-effects. First line of acute treatment is sumatriptan administered subcutaneously[7,8,9] and inhalation of 100% oxygen.[10,11,12,13] Preventive therapies are subdivided into maintenance and transitional treatments. Transitional treatment is often used to relieve the patient until maintenance prophylactic is adequately titrated and consists of oral steroids or greater occipital nerve (GON) blocks.[14,15] Maintenance treatment aims to reduce attack frequency with verapamil being first-choice, but only 50-80% of CH patients are responders;[16] and its use is hampered by side-effects since many patients need high doses. Other preventive treatments are less attractive due to their side-effect profile, the scarcity of evidence[17,18] and high cost.[19] In the clinic, several types of treatment are combined in the effort to provide relief to the patients and increase the quality of life.

Increased plasma or serum levels of calcitonin gene-related peptide (CGRP) have been associated with painful syndromes such as migraine and cluster headache.[20] Cluster headache patients have higher CGRP-levels compared to migraine patients and healthy controls.[21] As in migraine,[22] CGRP levels are altered during attacks. Recently, a provocation study supported the central role of CGRP involvement in CH as infusion of CGRP induced attacks in 89% of episodic CH patients in an active bout.[23]

Eptinezumab is a humanized monoclonal antibody that inhibits the action of calcitonin gene-related peptide (CGRP) and is approved by the Food and Drug Agency (FDA) as the first and only intravenous preventive treatment for migraine. Eptinezumab is administered by IV infusion every 12 weeks offering a route of drug administration with 100% bioavailability that allows for rapid CGRP inhibition. Eptinezumab IV infusion administered every 12 weeks by a healthcare professional helps to ensure treatment adherence and delivery of a known quantity of drug with each dose. In clinical studies, treatment with eptinezumab has been associated with a robust and clinically meaningful migraine reduction as early as the day after the first infusion, a sustained efficacy throughout the treatment period and an acceptable tolerability profile with low incidences of study drug withdrawal due to adverse events.

The following sections 1.1.2 and 1.1.3 provide a brief overview of the nonclinical and clinical data currently available for eptinezumab. Refer to the current version of the *Investigator's Brochure*[24] for more detailed information.

1.1.2 Nonclinical Data

Data from the comprehensive program of nonclinical studies support the clinical mechanism of action and safety of eptinezumab.

To demonstrate the ability of eptinezumab to block CGRP-driven vasodilation in vivo, several primary pharmacodynamic animal studies were conducted in rat, cynomolgus monkey and rabbit. The administration of eptinezumab was well tolerated at doses up to 100 mg/kg, the highest dose administered, and inhibited increases in dermal blood perfusion induced by either topical capsaicin (rats and monkey) or intradermal β-CGRP challenge (rabbit). The pharmacodynamic effects were dose-dependent and occurred from 0.1 mg/kg. The appropriateness of the nonclinical species has been established in vitro (rat and rabbit). Across species (including human), eptinezumab has a binding affinity in the low picomolar range for α-and β-CGRP and has been shown to functionally inhibit α-and β-CGRP with high specificity.

Intravenous administration of eptinezumab, either as a single- or multiple-dose for 1-month duration up to 100 mg/kg/dose in rats or monkeys, or multiple-dose for 6-months duration up to 150 mg/kg/dose in monkeys, was well tolerated. No mortality or adverse findings attributed to the pharmacological activity of eptinezumab were observed in the single- or repeat-dose studies in rats or cynomolgus monkeys. As determined during a 6-month chronic toxicity in cynomolgus monkeys, the NOAEL of 150 mg/kg/dose supports a 103-fold or 123-fold safety margin by C_{max} or AUC for the highest dose, 300 mg, of eptinezumab administered by IV infusion every 12 weeks in humans.

Overall, following IV administration in the nonclinical studies, eptinezumab exposure was generally dose proportional, and the plasma-concentration profiles were consistent for IV administration with the rapid achievement of C_{max} followed by a mono-exponential decline. The volume of distribution (V_c) for eptinezumab is generally limited to the vascular compartment.[24]

Eptinezumab is unlikely to interact directly with DNA or other chromosomal material, and under ICH S6(R1) guidance, evaluations for potential genotoxicity were considered unnecessary and were not performed for eptinezumab. Based on extensive evaluation of the literature related to inhibition of CGRP, angiogenesis, and tumor growth as well as the absence of eptinezumab-related proliferative findings from long-term studies in monkeys, no further nonclinical studies addressing the carcinogenic risk are considered necessary.

In conformance with applicable guidance documents, a complete package of reproductive/development toxicity studies were conducted. In these studies, administration of eptinezumab by intravenous injection to pregnant female rats or rabbits at 75 or 150 mg/kg/dose was well tolerated. No effects on male or female reproductive function or performance, fertility or early embryonic development in rats were observed. No parental effects or evidence of embryo-lethality, fetotoxicity, or teratogenicity in rats or rabbits were observed. There were no effects on the survival, physical development, behavior or reproductive performance of the F1 generation in the pre- and postnatal development study in rats.

The local tolerance of eptinezumab was assessed following multiple dose studies in rats and cynomolgus monkeys utilizing eptinezumab administered IV. No gross observations including erythema and edema, or toxicologically significant histological changes at the injection site(s) were noted in either species for any dose route at concentrations up to 100 mg/mL eptinezumab.

Biologics in general have minimal risks regarding drug-drug interactions;[25] therefore, drug interactions with eptinezumab and concomitant medications are not expected, and nonclinical studies evaluating the potential for interactions with drugs that may be co-administered with eptinezumab were not performed.

1.1.3 Clinical Data

The clinical program of eptinezumab is composed of 5 completed studies to date; 4 studies are placebo-controlled (Phase Ib study in frequent episodic migraine (ALD403-CLIN-002),[26] Phase II study in chronic migraine (ALD403-CLIN-005),[27] PIII study in frequent episodic migraine (ALD403-CLIN-006),[28] PIII study in chronic migraine (ALD403-CLIN-011)[29] and 1 study is open-label (PIII study in chronic migraine (ALD403-CLIN013)).[30,31] Phase III study (18903A)[32] is ongoing to assess treatment of eptinezumab in patients experiencing an acute attack of migraine. A further Phase I study is initiated to assess the safety and PK in Japanese healthy volunteers (18899A).

Eptinezumab is administered by 30-45 minute IV infusion, which bypasses extravascular absorption routes and renders 100% bioavailability. The time required to achieve therapeutic concentrations for eptinezumab is rapid and maximum observed plasma concentration (C_{max}) is typically observed at the end of infusion. The low plasma clearance (0.15 L/d) and protracted terminal-elimination half-life ($t_{½}$) of 27 days for eptinezumab support a sustained duration of effect and infrequent, once every 12 weeks dosing in migraine preventive treatment. The mean accumulation ratios based on C_{max} and $AUC_{0\text{-}tau}$ are 1.08 and 1.15, respectively.

Eptinezumab is not metabolized by cytochrome P450 enzymes. Therefore, interactions by eptinezumab with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are considered unlikely.[33] Nevertheless, the co-administration of eptinezumab in combination with sumatriptan was investigated in Study ALD403-CLIN001.[24] The co-administration of sumatriptan did not appear to alter the single dose PK of eptinezumab. Similarly, the PK of sumatriptan was not impacted upon by the co-administration of eptinezumab.

Results from the two pivotal, placebo-controlled, Phase III trials showed that eptinezumab at doses of 100 mg or 300 mg administered by IV infusion every 12 weeks (2 infusions) led to significant reductions in monthly migraine days in patients with episodic or chronic migraine (ALD403-CLIN-006 and ALD403-CLIN-011).[28,29] Both eptinezumab 300 mg and 100 mg groups achieved the primary efficacy endpoint and all key secondary endpoints in the prespecified statistical hierarchy. The therapeutic benefit resulting from administration of eptinezumab for the preventive treatment of migraine in adults is robust and clinically meaningful, as demonstrated by the results of the 75% and 50% migraine responder analyses. Administration of eptinezumab 100 or 300 mg resulted in a rapid, migraine preventive effect that was established on the day after the first infusion and maintained over the 12-week dosing cycle. Both eptinezumab doses were associated with a consistent pattern of statistically significant and clinically meaningful efficacy across these endpoints compared with placebo.

The safety of eptinezumab has been evaluated in more than 2,400 subjects in doses up to 1000 mg. Long-term data with eptinezumab is limited; however, in study ALD403-CLIN-013 a total of 100 patients have been treated with the 300 mg dose and completed the study at Week 104 and no new significant findings have been identified during the long-term follow up. In patients with migraine, nasopharyngitis and hypersensitivity reactions, including anaphylactic reactions, are considered adverse drug reactions for eptinezumab. In the pivotal Phase III studies (ALD403-CLIN-006 and ALD403-CLIN-011) hypersensitivity reactions were reported with multiple related adverse event terms, such as hypersensitivity, angioedema, urticaria, flushing/hot flush, rash and pruritus. These events were reported in approximately 4% of patients on 300 mg eptinezumab, 3% of patients on 100 mg eptinezumab and 1% of patients on placebo. Serious hypersensitivity reactions have been reported, including anaphylactic reactions on rare occasions. In most cases, the events developed during or within minutes of the infusion and subjects recovered following drug discontinuation and adequate treatment.

The safety findings to date indicate that eptinezumab is well tolerated and demonstrates a favorable risk-benefit profile based on review of nonclinical, clinical, and scientific literature data.

1.2 Rationale for the Study

Cluster headache is an excruciatingly painful primary headache disorder, which places an exceptional burden on those affected. Few, if any, medical disorders are more painful than cluster headache. Patients describe the pain of a single attack as being worse than anything

else they have experienced. The severity of the pain has earned it the sobriquet “suicide headache,” although this is a rare occurrence in this exceptional patient group.

There are significant unmet needs for just about every clinical aspect of the patient with cluster headache, particularly related to the severity of the disease and treatment options. Most patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable (using a Visual Analog Scale 10 cm scale).[6]

Due to the high unmet need for new, effective, fast onset and better tolerated therapies for episodic cluster headache, Lundbeck is planning to conduct this global Phase III clinical study.[34] The study will allow the evaluation of treatment effects, including safety, and is intended to show a statistically significant effect on number of attacks during the cluster headache bout. The results from the Phase III study with galcanezumab in episodic cluster headache,[35] and its approval by the FDA in this indication, prove the principle that mAbs, targeting CGRP, provide clinical benefit in episodic cluster headache. Thus eptinezumab, which has similar biological properties and a documented faster onset of action in patients with migraine, is considered a viable therapeutic option to provide a fast reduction in the number of cluster headache attacks in patients with episodic cluster headache.

2 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 3.

Panel 3 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of eptinezumab in patients with eCH	**Primary endpoint:** Change from Baseline in the number of weekly attacks (Weeks 1–2) **Key secondary endpoints:** • Response: ≥ 50% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2) • Change from Baseline in the number of daily attacks (Days 1-3) • Change from Baseline in the number of weekly days with < 3attacks per day (Weeks 1-2) • Time from first infusion of IMP to resolution of cluster headache bout (within the first 4 weeks) • Number of attacks starting <= 24 hours after the start of the first infusion of IMP
	Secondary endpoints: • Change from Baseline in the daily mean score on 5-point self-rating pain severity scale (Days 1- 3) • Change from Baseline in the number of weekly attacks (Week 1) • Change from Baseline in the number of weekly attacks (Week 2)

Objectives	Endpoints
	• Response: ≥50% reduction from Baseline in the number of weekly attacks (Week 1) • Response: ≥30% reduction from Baseline in the number of weekly attacks (Week 1) • Response: ≥30% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week) • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 1) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Week 2) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week) • Change from Baseline in the number of weekly attacks (Weeks 1- 4) • Change from Baseline in the weekly integrated measure of frequency and intensity of pain (Weeks 1-4) (that is, the sum of the intensity (worst pain on a 5-point self-rating pain severity scale) for each attack during that week). • Change from Baseline in the mean score on 5-point self-rating pain severity scale (average per attack over a week) for each of Weeks 1, 2, 3, and 4 • Change from Baseline in the number of weekly attacks for each of Weeks 3 and 4 • Patient Global Impression of Change (PGIC) score at each of Weeks 1, 2, and 4 • Change from Baseline in the Sleep Impact Scale (SIS) domain scores at each of Weeks 2 and 4
	Exploratory endpoints: • Response: 75% reduction from Baseline in the number of weekly attacks (Weeks 1-2) • Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-4) • Time from first infusion of eptinezumab to resolution of cluster headache bout (within the first 16 weeks; only for patients randomized to eptinezumab at Baseline) • Use (yes/no) of abortive medication (triptans or O2) for each of Weeks 5 to 16 • Use (yes/no) of preventive medication for each of Weeks 1 to 16 • Use (yes/no) of transitional treatment for each of Weeks 5 to 16 • Number of attacks starting <= 24 hours after the start of the first infusion of IMP divided into three parts: one for attacks starting >0 and <= 8 hours after the start of the first infusion of IMP, one for attacks starting >8 and <=16 hours after the start of the first

Objectives	Endpoints
	infusion of IMP, and one for attacks starting >16 and <=24 hours after the start of the first infusion of IMP • Change from Baseline in the EQ-5D-5L Visual Analogue Scale (VAS) score at Weeks 8 and 16 • Patient Global Impression of Change (PGIC) score at Weeks 8 and 16 • Number of weekly attacks for each of Weeks 5 to 16 • Severity of pain (average per attack over a week) based on a 5-point self-rating pain severity scale for each of Weeks 5 to 16
Secondary Objectives • To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity	**Secondary endpoints:** • Change from Baseline in EQ-5D-5L Visual Analogue Scale (VAS) at Weeks 2 and 4 • Health Care Resources Utilization (HCRU) at Baseline and Week 4 • Change from Baseline in the Work Productivity Activity Questionnaire: General Health second version (WPAI:GH2.0) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Week 4
Safety Objectives • To evaluate the 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

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[36]

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

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[37] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

304 patients will be randomly allocated via a randomization system to one of the two initial treatments: eptinezumab 400 mg, or placebo, in a ratio of 1:1 (152 patients in the eptinezumab 400 mg group and 152 patients in the placebo group). The randomization has been stratified

by country as the number of patients (app. 300) compared to the number of sites (>100) would yield a number of sites with very few patients (and therefore an imbalance in the randomization between the two sequences) if the stratification was done by site.

The target population for this study is defined as patients with eCH, based on the IHS ICHD-3 classification, with an adequately documented record or reliable history of eCH prior to Screening Visit 1 and confirmed via prospectively collected information in the eDiary during Screening Period 2. The study is planned as a global study.

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

The patients can be screened up to 12 months prior to the Screening Period 2. The patients will enter Screening Period 2 as soon as possible after they experience the beginning of a cluster headache bout, which is characterized by the presence of at least one typical cluster headache attack, and not later than 1 week after the start of the first attack. Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enrol this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient.

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

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

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

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

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

Eligibility will be assessed during Screening Period 1, during Screening Period 2, as well as before the administration of IMP at the Baseline Visit (Day 0/Visit 3) as described in Panel 2.

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

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

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

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

Blood samples for IMP quantification will be collected at regular intervals during the study (Panel 2) and results will be reported separately.

Patients in the study will have access to appropriate medical care in accordance with normal clinical practice after they complete or withdraw from the study.

Assessments performed in a subset of patients:

Blood sampling for pharmacogenetics is optional. Refer to Panel 2.

Interim Analysis:

An interim futility analysis that is unblinded to a study independent team, evaluating efficacy, will be performed based on 204 randomized and treated patients who have had the chance of completing the Visit 6 (Week 4). Randomized patients with an infusion on the same date, but after 204 patients have been treated, will also be included. The interim analysis will be performed for the APTS_IN. If the estimated treatment effect is less than 1/3 of the expected effect size (3.00/3 = 1), a decision will be made to either continue the recruitment, or to end enrolment.

The interim analysis will be performed by an independent CRO.

The independent CRO will inform a predefined group of Lundbeck employees whether the criterion for the interim futility have been met or not. No further details of the interim analysis results will be provided.

Details of information flow and the interim process will be described in a separate interim analysis charter.

Details of the statistical analysis for the interim analysis will be described in an interim statistical analysis plan.

3.2 Rationale for the Study Design

The current study is planned as a placebo-controlled study with delayed-start design. It includes a 4-week double-blind, randomized Placebo-controlled Period to investigate whether eptinezumab can lead to clinically significant improvement in patients with episodic cluster headache. The duration of the Placebo-controlled Period and the selection of the time for the primary outcome measure is in line with the Guidelines of the *International Headache Society* for controlled trials of drugs in cluster headache[38] and is based on the published results with galcanezumab in episodic cluster headache.[35] All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (placebo or eptinezumab 400 mg) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patient randomized to placebo will receive eptinezumab 400 mg. Thus, the delayed-start design provides an opportunity for all study participants to receive treatment with eptinezumab. The duration of Screening Period 1 is chosen, based on the natural history of the disease and is intended to ensure that patients with a history of episodic cluster headache progress to Screening Period 2 in the moment they enter in a cluster bout and reach the required level of cluster headache attacks activity. The Screening Period 2 duration is chosen to allow (i) enough time for collection of prospective data on cluster headache activity and (ii) enrolment of patients who are predicted to still be in a bout for at least six more weeks.

The proposed study population for this study are patients with episodic cluster headache in a bout. This target population corresponds largely to the patient population in the completed Phase III study with galcanezumab in which galcanezumab demonstrated positive benefit / risk profile and is considered representative for patients with episodic cluster headache in need of treatment.[35]

The primary endpoint is the change from Baseline in the number of weekly attacks (Weeks 1-2) and will be evaluated at Week 2. Based on the Guidelines of the *International Headache Society* for controlled trials of drugs in cluster headache,[38] the published results with galcanezumab in episodic cluster headache[35] and the documented faster onset of action of eptinezumab in patients with migraine, this is expected to be an adequate duration to investigate the efficacy of eptinezumab. Secondary endpoints evaluating the effect on speed of onset, sleep disturbances, health-related quality of life, as well as work productivity, are included in the study to evaluate the impact of treatment beyond the reduction in number of cluster headache attacks. The sample size for the primary endpoint is chosen based on the

phase III data with galcanezumab in patients with episodic cluster headache and should provide adequate power for detection of a clinically meaningful treatment effect. An interim futility analysis that is unblinded to a study independent team, evaluating efficacy, will be performed based on 204 randomized and treated patients who have had the chance of completing the Visit 6 (Week 4/). Randomized patients with an infusion on the same date, but after 204 patients have been treated, will also be included. Based on the interim analysis result of the primary endpoint, a decision will be made to either continue the recruitment, or to end enrolment.

Fulfilment of criteria for eCH, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the Screening period 2 (i.e., frequency of minimum 7 and maximum of 56 CH attacks for the 7-day Screening Period 2). The lower and the upper limit for CH attack frequency is in line with the IHS ICHD-3 criteria for CH. Clinical site staff will be given access to the eDiary data. Prior to enrolment, the investigator will review the data in the *eDiary Eligibility Report* to determine if the eligibility criteria are fulfilled.

The dose of 400 mg eptinezumab is recommended, based on the fact that cluster headache patients have higher CGRP-levels compared to migraine patients and healthy controls,[21] suggesting that a higher dose of eptinezumab is needed to alleviate features of the disease, related to the CGRP pathobiology. This is in line with the design of the galcanezumab trial in episodic cluster headache[35] which investigated the efficacy and safety of a dose, higher, compared to the approved galcanezumab dose for the treatment of migraine.[39,40]

The placebo group is representative of the best supportive care (BSC) as the study allows abortive therapy for cluster headache. Thus, the study will compare the efficacy of eptinezumab and BSC versus BSC alone.

During the Placebo-controlled Period of the study the patients will be randomly allocated to one of two treatment arms of either 400 mg eptinezumab, or placebo with a randomization ratio of 1:1. Inclusion of a placebo group is justified since the group is representative of the best supportive care (BSC), allowing abortive therapy of the cluster headache attack. Thus, the study will compare the efficacy of eptinezumab and BSC versus BSC alone. All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (placebo or eptinezumab 400 mg) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patient randomized to placebo will receive eptinezumab 400 mg. Given the eptinezumab half-life and proven efficacy over 12 weeks in migraineurs, all patients will be exposed to eptinezumab during the Active Treatment Period. Preventive treatments (transitional and maintenance) can be initiated after the end of the Placebo-controlled Period; hence no patient will be denied access to standard treatments in this study.

Blood sampling will be required at several time points during the study to evaluate standard safety laboratory parameters, ADA including NAbs.

3.3 Benefit-Risk Assessment

Benefits

It has been shown that mAbs targeting CGRP provide clinical benefit in patients with episodic cluster headache.[35] Therefore, eptinezumab, which is also a mAb targeting CGRP with documented fast onset of action in patients in need of preventive treatment for migraine, is considered a viable therapeutic option to provide a fast reduction in the number of cluster headache attacks in patients with eCH. The intravenous formulation offers a route of administration with 100% bioavailability that allows for rapid CGRP inhibition.

Risks

No safety data, specific to the use of eptinezumab in patients with cluster headache is available. However, the safety of eptinezumab has been investigated in over 2,400 healthy subjects and patients with migraine at doses up to 1000 mg and the analyses show that eptinezumab is safe and well tolerated (see the current version of the Investigator's Brochure[24] for more detailed information). No important identified risks or important potential risks that could alter the benefit-risk profile of eptinezumab have been identified to date. Nasopharyngitis and hypersensitivity reactions, including anaphylactic reactions, are considered adverse reactions for eptinezumab. In the pivotal studies in migraine, hypersensitivity reactions were reported with multiple related adverse event terms, such as hypersensitivity, angioedema, urticaria, flushing/hot flush, rash and pruritus. Most hypersensitivity reactions occurred during the infusion and were not serious. Serious hypersensitivity reactions have been reported, including anaphylactic reactions on rare occasions. In all cases, the patients recovered upon standard of care treatment.

With regard to the safety of the eptinezumab 400 mg dose, the safety of eptinezumab in patients with migraine and in healthy subjects has been explored at doses up to 1000 mg, with no observable difference in the safety profile compared to the eptinezumab 100 mg and 300 mg doses, which are the doses approved by the US FDA and in Canada for preventive treatment of migraine. In addition, the long-term treatment effects of eptinezumab 400 mg will be evaluated in an open-label study in patients with chronic Cluster Headache (study 19385A).

The safety of study subjects is monitored throughout the study via periodic collection of adverse events, vital signs, laboratory tests, ECGs and other safety assessments such as evaluation of the suicidality (C-SSRS). Although there was no evidence of impact of ADA development on efficacy or safety in any of the previous clinical studies, in the current study blood sampling for ADA including NAbs will be assessed prior to the first eptinezumab infusion, at Weeks 16 and 24 (Safety Follow-up), and at Withdrawal Visit when applicable. To monitor patient safety, safety data will be reviewed on an ongoing basis and evaluated regularly by the Lundbeck Safety Committee. This will ensure that prompt actions are taken, if needed.

Risk-mitigation

Based on the biological plausibility and the inherent risk, hypersensitivity reactions are possible with any infused protein.[41] In order to minimize the risk of hypersensitivity reactions due to the higher dose of eptinezumab (400 mg considered justified in patients with cluster headache based on the higher CGRP levels) compared to doses used in migraine (100 mg or 300 mg), the minimum duration of the eptinezumab infusion must be 45 minutes (45 + 15 minutes, according to the study protocol).

Furthermore, eptinezumab is administered in a clinical facility at the study site under medical supervision with appropriate measures for adequate treatment in place. Per protocol, patients are required to be monitored during the infusion and for a period of 1 hour from the end of infusion. Patients will be requested to stay longer should the investigator determine this is clinically warranted.

In addition to the above, the following risk mitigations are also taken for hypersensitivity reactions:

- History of severe drug allergy or hypersensitivity or known hypersensitivity to IMP/excipients is an exclusion criterion.
- Serious/severe hypersensitivity is a criterion for withdrawal from treatment.

In the context of the coronavirus disease 2019 (COVID-19), Lundbeck and the CRO will continue to follow each participating country's guidance for travel, social distancing, minimum number of people in an indoor location at any time, personal protective equipment, and remote consenting procedures. Should further restrictions be imposed in any country that could impact patients' ability to attend visits, and/or clinical site staff's ability to continue to resource the study to an adequate level, Lundbeck and the CRO will adapt their approach to patient enrolment and return visits. These mitigations may include, but not limited to:

- Including a home nursing vendor to ensure the continuation of IMP Visits, including eptinezumab administration and post-infusion monitoring (if logistically possible and acceptable by the country-specific law). The administration via the home nursing vendor will have the same medical supervision and equipment/treatment in place needed to ensure patient's safety as similar to the clinical facility at the study site.
- Risk assessment (per country or site level) of enrolling new patients.

Benefit-Risk Assessment

Cluster headache is an excruciatingly painful primary headache disorder, which places an exceptional burden on those affected. There are significant unmet needs for the patient with cluster headache, particularly related to the severity of the disease and the lack of available fast onset, and better tolerated therapies.

The safety of eptinezumab, as investigated in patients with migraine and in healthy volunteers, shows that eptinezumab is safe and well tolerated. The risks for study subjects are further mitigated by measures in the protocol and safety monitoring of study subjects throughout the study.

Sponsor considers the benefit-risk profile of Study 19386A to be acceptable based on the nonclinical and clinical data for eptinezumab.

4 Ethics

4.1 Ethical Rationale

This study will evaluate eptinezumab as a potential therapeutic candidate for a target patient population with episodic cluster headache in a bout.

Inclusion of placebo group is justified since the group is representative of the best supportive care (BSC). During the Placebo-controlled Period of the study patients will be randomly allocated to one of two treatment arms of either 400 mg eptinezumab, or placebo with a randomization ratio of 1:1. Inclusion of a placebo group is justified since the group is representative of the BSC, allowing abortive therapy of the cluster headache attack. Thus, the study will compare the efficacy of eptinezumab and BSC versus BSC alone. All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (placebo or eptinezumab 400 mg) in a blinded manner, so that patients previously exposed to eptinezumab will receive placebo and patient randomized to placebo will receive eptinezumab 400 mg. Given the eptinezumab half-life and proven efficacy over 12 weeks in migraineurs, all patients will be exposed to eptinezumab during the Active Treatment Period. Transitional and preventive therapies can be initiated after the end of the Placebo-controlled Period; hence no patient will be denied access to standard treatments in this study.

The dose of 400 mg eptinezumab is recommended, based on the fact that cluster headache patients have higher CGRP-levels compared to migraine patients and healthy controls,[21] suggesting that a higher dose of eptinezumab is needed to alleviate features of the disease, related to the CGRP pathobiology. This together with data from previous studies,[24] in which eptinezumab was dosed up to 1000 mg and without any major safety findings, support that eptinezumab 400 mg can be safely used in the current study. The published results of the galcanezumab trial in episodic cluster headache[35] which investigated the efficacy and safety of a dose, higher, compared to the approved galcanezumab dose for the treatment of migraine do not suggest any safety concerns and provide further support for the dose selection.[39,40]

The patients will be fully informed about the study, including the risks and benefits of their participation in the study.

The patient may withdraw from the study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the patient is otherwise entitled. Unscheduled visits can be made, and immediate withdrawal is possible. Throughout the study, signs of suicidal risk will be assessed and the patients at risk will be withdrawn from the study.

In general, safety data with eptinezumab have not raised any clinical safety concerns from the completed phase III studies in migraine. However, it cannot be ruled out that the IMP could have adverse effects that have not yet been reported. Blood sampling will be required at

several time points during the study to evaluate standard safety laboratory parameters. Although there was no evidence of impact of ADA development on efficacy or safety in any of the previous clinical studies, in the current study the ADA response will be assessed prior to the first IMP infusion, at Weeks 16 and 24 (Safety Follow-up). To monitor patient safety, safety data will be reviewed on an on-going basis and evaluated regularly by the *Lundbeck Safety Committee*. This will ensure that prompt actions are taken, if needed.

The risks associated with this study are considered adequately elucidated in the nonclinical and clinical studies, well controlled by cautionary measures in the study design, and well-balanced with the potential benefits of the treatment with eptinezumab, a potentially effective treatment for episodic cluster headache.

In accordance with *Good Clinical Practice*,[37] qualified medical personnel at Lundbeck or the clinical CRO will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the *Lundbeck Safety Committee* to ensure that prompt action is taken, if needed.

In accordance with *Good Clinical Practice*,[37] the investigator will be responsible for all study-related medical decisions.

Information on race will be collected, if allowed according to the country-specific law. Collecting information on race will allow the evaluation of treatment effects including safety evaluations in the overall population as well as investigations of the potential impact of intrinsic and extrinsic factors (as described in Ethnic Factors in the Acceptability of Foreign Clinical Data ICH E5(R1) Guideline).[42]

Risks Related to the Coronavirus Disease 2019

Sponsor and CRO have performed a review of the protocol, the participant population, and study design and conclude that the risks with regards to the COVID-19 are minimized both for patients participating in the study and clinical site staff conducting the study in line with the US FDA and EMA guidelines.[43,44] The risks for the patients remain well controlled and balanced with the potential benefits of the treatment. This is based on the following:

- Patients participating in the clinical study will not attend visits in an area of the hospital that would be high risk for COVID-19 patients to be treated or seen.
- The protocol has flexibility for re-screening and Screening Period extension to further enable sites and patients to continue the trial in case of quarantine or lockdowns.
- Patient visits to site will be limited to six on-site visits over a time span of 6 to 18 months (depending on the patient's time of next bout) and all further contact will be conducted by phone. In exceptional situations, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and IMP administration, while the remaining assessments (eDiary, ePROs, C-SSRS, and investigator evaluations) can be conducted remotely via a virtual clinic visit. Consequently, this reduces the burden on the clinical trial

site to manage recurring visits around the potential restrictions for number of people allowed on site at any one time.
- Study allows the flexibility at Screening Visit 1 to allow for review and signature of *Informed Consent Form(s)* via virtual clinic visit and Screening Visit 1 assessments may be extended over several days, if needed. For other visits, patients are allowed to complete all their eDiary and ePROs in the remote setting (that is, at home), thus reducing the time that the patient needs to spend on site and minimizing burden for site staff at a given visit.
- The percentage of on-site targeted source data verification required for the study is approximately 30%, which, along with the number of visits for this study, substantially decreases the amount of time clinical research associates (CRAs) are expected to spend on site. Further, remote source data verification is allowed in some cases as described in section 12.
- Patients will be tested for COVID-19 as needed, according to country-specific requirements.

Sponsor and CRO will continue to follow each participating country's guidance for travel, social distancing, minimum number of people in an indoor location at any time, personal protective equipment, and remote consenting procedures. Should further restrictions be imposed in any country that could impact patients' and CRAs' ability to attend visits, and/or clinical site staff's ability to continue to resource the study to an adequate level, Sponsor and CRO will adapt their approach to patient enrolment, return visits and data monitoring by CRAs. These mitigations will include, but not limited to:
- Including a home nursing vendor to ensure the continuation of IMP Visits (if logistically possible and acceptable by the country-specific law). The administration via the home nursing vendor will have the same medical supervision and equipment/treatment in place needed to ensure patient's safety as similar to the clinical facility at the study site.
- An adaptation of the on-site data monitoring scheme to increase remote monitoring and consideration of remote source data verification.
- Risk assessment (per country or site level) of enrolling new patients.

Any adaptations to the already approved protocol procedures and monitoring approach will be implemented in line with the US FDA and EMA guidances.[43, 44]

Sponsor and CRO will assess on a site-by-site basis whether restrictions, either at a country or site level, would mean it would not be within the best interest of the potential patient or the clinical site staff to activate the study at a particular time point. This would be based on, but not limited to, the following:
- Country/area lockdowns.
- A site's ability to undertake non-essential clinic visits.
- A site's ability to adequately resource the study.
- CRO implemented restrictions for employee safety for travel and on-site visits.

4.2 Informed Consent

No study-related procedures, including any Screening Visit 1 procedures, may be performed before the investigator has obtained written informed consent from the patient.

It is the responsibility of the investigator, or person designated by the investigator, to obtain written informed consent from the patient. If the informed consent process may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

At Screening Visit 1, the patient will be asked to sign the:

- Main *Informed Consent Form*
- *Informed Consent Form* for blood sampling for pharmacogenetics (optional)

Under exceptional circumstances, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, the discussion with the patients about the *Informed Consent Form(s)* can be done as a virtual clinic visit and the *Informed Consent Form(s)* can be provided remotely in line with the US FDA and EMA guidances.[43, 44] According to the EMA guidance, this could comprise contacting the patients via phone or video-calls and obtaining oral consents, to be documented in the patients' medical records, supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the patients are back at the clinical sites.[44]

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

If a patient does not enter a cluster bout during the maximum duration of Screening Period 1 (52 weeks), the site may request a 6-month extension of the Screening Period 1. If an extension is not requested or if an extension has been requested but not granted, the patient is considered a screen failure. If, after the 6-month extension has expired, the patient would still like to participate in the study and the study is still enrolling new patients, the patient is a screen failure and must sign new informed consent form(s) and will complete Screening Visit 1 again.

If the study completes enrolment or is terminated early due to the results of the interim analysis and the patient has not entered a cluster bout during Screening Period 1, the patient is considered a screen failure and will not be asked to attend any further study visits. If the study completes enrolment or is terminated early due to the results of the interim analysis and the patient is in Screening Period 2, the patient will continue in the study.

Re-screening of Screening Visit 1 and re-screening or extension of Screening Visit 2 is allowed under certain circumstances. Refer to section 8.3.3, 8.3.4, and 8.3.5.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether

it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to the patients the aims and methods of the study and any reasonably expected benefits and foreseeable risks or inconveniences to the patients.

The patients must be informed:

- that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision
- of the possibility of withdrawing consent (section 8.9)
- of their right to request a copy of their personal data from the study via the investigator
- of their right to be informed by the investigator, after the study has been reported, about which treatment they received
- of their right to receive information about the study results from the investigator on the patients' own initiative; the results will be available approximately 1 year after the end of the study

The patients must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ethics committees (ECs) or institutional review boards (IRBs)) may view their medical records. The patients must also be informed that de-personalized copies of parts of their medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ECs or IRBs) for verification of study procedures and/or data. The confidentiality of the patients will in all cases be respected.

The patients must be given ample time and opportunity to enquire about details of the study prior to deciding whether to participate in the study.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients. Prior to allowing a patient to participate in the study, an *Informed Consent Form(s)* must be signed and dated by the patient and signed and dated by the investigator or a designee on the same day. The patients must be given a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form(s)*.

The consent procedures described above will only be implemented if allowed by local law and regulations and will only be initiated after approval by the relevant ECs or IRBs.

As the blood sampling for the exploratory genomic, proteomic, and metabolomic analyses, including blood sampling for possible future ADA assessment and future exploratory biomarkers, is an integral part of this study, the main *Informed Consent Form* covers these analyses. Conversely, the blood sampling for pharmacogenetics is optional and a separate *Informed Consent Form* covers this analysis.

The blood samples for potential future exploratory biomarker analysis, or the data derived from these blood samples, may be shared with academic and public institutions and other companies. However, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Informed Consent Form* and a *Material Transfer Agreement.*

Country-specific pregnancy ICF: see section 10.2.

A patient may, at any time and without stating a reason, specifically request the destruction of the patient's DNA sample, irrespective of the patient's continued participation in the study. The investigator must send a written request on behalf of the patient to the International Study Manager. The investigator will receive written confirmation from Lundbeck when the DNA sample has been destroyed.

4.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the Danish Data Protection Act and the European Union legislation[45] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organization to ensure compliance with the above-mentioned legislation.

4.4 Ethics Committees and Institutional Review Boards

This study will be conducted only after Lundbeck has received confirmation that the regulatory authorities have approved or confirmed notification of the study and that written approval of the protocol has been granted by the appropriate EC or IRB.

The investigator must not allow any patients to participate in the study before receiving confirmation from Lundbeck or the CRO that the required approvals and/or notifications have been received.

The EC or IRB must be informed when specific types of protocol amendments have been made and written approval must be obtained before implementation of each amendment, if required by local law.

If applicable, interim reports on the study and reviews of its progress will be submitted to the EC or IRB by the investigator at intervals stipulated in its guidelines.

5 Study Population

5.1 Number of Patients and Regions

Planned regions:	Europe, North America, and Japan
Planned number of screened patients (approximately):	760
Planned number of randomized patients:	304

5.2 Patient Recruitment

Competitive patient recruitment between sites will be used during the entire recruitment period to ensure that the required number of patients are randomized within the planned recruitment period.

The investigators will be notified immediately when the recruitment period comes to an end. When the study completes enrolment or if the study is terminated early due to the results of the interim analysis, any patients who are in Screening Period 1 will be considered a screen failure and will not be asked to attend any further study visits and any patients who are in the Screening Period 2 will continue in the study.

5.3 Selection Criteria

Patient selection is based on the inclusion and exclusion criteria listed below.

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

The eligibility of patients who occasionally use cannabinoids (confirmed by either anamnesis or finding at Urine drug screen at Screening Visit 2) must be based on a confirmation from the investigator that the patient does not meet Exclusion criteria 10, 24 and 25.

Patients who meet each of the inclusion criteria and none of the exclusion criteria at the Screening Visit 2 and Baseline Visit (Day 0/Visit 3) are eligible to participate in this study. Refer to Panel 2.

Inclusion Criteria

1. The patient is able to read and understand the *Informed Consent Form(s).*

2. The patient has signed the *Informed Consent Form(s).*
3. [Inclusion Criterion 3 removed from protocol edition 2.0].
4. The patient is willing and able to attend study appointments within the specified time windows.
5. The patient is an outpatient.
6. The patient has adequate venous access for administration of study drug.
7. The patient has episodic cluster headache, as defined by IHS ICHD-3 classification,[1] (see section 9.1.2) with an adequately documented record or reliable history of eCH of at least 12 months prior to Screening Visit 1.
8. The patient has a medical history of first symptoms of cluster headache from ≤60 years of age.
9. The patient has an adequately documented record or reliable history of previous acute and preventive medication use for eCH, for at least 12 months prior to Screening Visit 1.
10. The patient has a prior history of cluster period(s) lasting 6 weeks or longer, when untreated.
11. The patient is able to distinguish cluster headache attacks from other headaches (i.e. tension-type headaches, migraine).
12. The patient is, at Screening Visit 2, in cluster headache bout, characterized by the presence of at least one typical cluster headache attack, that started not later than 1 week prior to Screening Visit 2. In the opinion of the investigator the cluster headache bout is likely to continue for at least another 6 weeks based on prior cluster period history. Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enroll this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient.
13. The patient has during Screening Period 2 based on prospectively collected information in the eDiary a weekly cluster headache attack frequency of a (*this requirement should not be shared with the patient*):
    - minimum of at least 7 total cluster headache attacks out of the 7-day Screening Period 2
    - maximum of 56 cluster headache attacks out of the 7-day Screening Period 2
14. The patient has demonstrated compliance with the eDiary by entry of data for at least 6 of the 7 days of Screening Period 2.
15. The patient is aged ≥18 and ≤75 years at Screening Visit 1.
16. The patient, if a woman, must:
    - have had her last natural menstruation ≥12 months prior to Screening Visit 1, OR
    - have been surgically sterilized prior to Screening Visit 1, OR
    - have had a hysterectomy prior to Screening Visit 1, OR
    - remain sexually abstinent, when this is in line with her preferred and usual lifestyle, OR
    - engage exclusively in same-sex relationships, OR
    - agree not to try to become pregnant during the study, AND

- use at least one of the below adequate contraception:
    - combined oral, intravaginal or transdermal hormonal contraception
    - progestogen-only oral, injectable or implantable hormonal contraception
    - intrauterine devices (IUD)
    - intrauterine hormone-releasing system (IUS)
    - barrier methods (such as male or female condom) with spermicide
    - vasectomized partner
- The contraception must be used from Screening Visit 1 to ≥6 months after the last dose of IMP.

17. The patient, if female, must have a confirmed negative blood pregnancy test at Screening Visit 2.
18. The patient agrees to have regular contact with another adult throughout the study (in the Czech Republic only).

[Country Specific Amendment 1 for Japan; revision of inclusion criterion 16:

The patient, if a woman, must:

- have had her last natural menstruation ≥12 months prior to Screening Visit 1, OR
- have been surgically sterilized prior to Screening Visit 1, OR
- have had a hysterectomy prior to Screening Visit 1, OR
- remain sexually abstinent, when this is in line with her preferred and usual lifestyle, OR
- engage exclusively in same-sex relationships, OR
- agree not to try to become pregnant during the study, AND
- use at least one of the below adequate contraception:
    - combined oral, intravaginal or transdermal hormonal contraception
    - progestogen-only oral, injectable or implantable hormonal contraception
    - intrauterine devices (IUD)
    - intrauterine hormone-releasing system (IUS)
    - male or female condom with or without spermicide
    - cap, diaphragm or sponge with spermicide
    - vasectomized partner
- The contraception must be used from Screening Visit 1 to ≥6 months after the last dose of IMP.]

Exclusion Criteria

1. The patient has previously been enrolled in this study and has received at least one IMP infusion.
2. The patient has experienced failure on a previous treatment targeting the calcitonin gene-related peptide (CGRP) pathway (anti-CGRP mAbs and gepants).
3. The patient has participated in a clinical study <30 days or has taken any investigational products within 5 plasma half-lives (whichever is longer) prior to Screening Visit 2.

4. The patient is a member of the study personnel or of their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
5. The patient is pregnant or breastfeeding.
6. The patient has a history of severe drug allergy or hypersensitivity or known hypersensitivity or intolerance to the IMP or its excipients.
7. The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, complex regional pain syndrome).
8. The patient has a history or diagnosis of hypnic headache, hemicrania continua, new daily persistent headache, chronic migraine or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura and migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
9. Patients with a lifetime history of psychosis, bipolar mania, or dementia are excluded. Patients with other psychiatric conditions whose symptoms are not controlled or who have not been adequately treated for a minimum of 6 months prior to Screening Visit 2 are also excluded.
10. The patient has a current diagnosis or history of substance abuse or alcohol abuse (DSM-5® criteria) <24 months prior to Screening Visit 2.
11. The patient has any other disorder for which the treatment takes priority over treatment of episodic cluster headache or is likely to interfere with study treatment or impair treatment compliance.
12. The patient has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that is, in the investigator's opinion, likely to affect central nervous system functioning.
13. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of IMP. Male patients with abnormal prostate-specific antigen (PSA) levels according to national/local guideline may be enrolled in the study provided they have been followed up, have been asymptomatic and have had no treatment for prostate cancer. Patients under surveillance for a low and stable level of M-component are allowed.
14. The patient has a history of clinically significant cardiovascular disease, including uncontrolled hypertension, ischaemia or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
15. The patient has or has had one or more of the following conditions that is/are considered clinically relevant in the context of the study: other neurological, pulmonary, hepatic, endocrinological, gastrointestinal, haematological, infectious, immunological or ocular disorder.
16. The patient has a history of epilepsy.
17. The patient takes or has taken recent or concomitant medication that is disallowed or allowed with restrictions (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of these medications during the study.
18. The patient has one or more clinically significant out-of-range vital signs at Screening Visit 2.

19. The patient has a Body Mass Index (BMI) ≥39 kg/m^2 at Screening Visit 2.
20. The patient has previously tested positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
21. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at Screening Visit 2, that are of potential risk to the patient's safety, or the patient has, at Screening Visit 2:
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
22. The patient has, at Screening Visit 2, an abnormal ECG that is, in the investigator's opinion, clinically significant.
23. The patient is, at Screening Visit 2, at significant risk of suicide (either in the opinion of the investigator or defined, using the C-SSRS, as the patient answering: "yes" to suicidal ideation questions 4 or 5 or answering: "yes" to suicidal behaviour within the past month). Patients who do not meet this criterion, but who are considered by the investigator to be at significant risk for suicide, are excluded.
24. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, or tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
25. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
26. The patient is hospitalized without consent or deprived of liberty due to a legal or administrative decision.
27. [Country-specific Protocol Amendment 1 for Czech Republic: The patient has poorly controlled hypertension, systolic blood pressure >160 mmHg and or diastolic blood pressure >100 mmHg.]
28. The patient is under legal guardianship and unable to provide his/her consent.
29. The patient is not covered by the national mandatory health insurance plan (when applicable according to country-specific law).

5.4 Withdrawal Criteria

A patient must be withdrawn from the study if:

- the patient withdraws consent (defined as a patient who **explicitly** takes back his or her consent); section 8.9 states how the patient's data will be handled
- the patient has been randomized in error*
- the patient fails to comply with study procedures
- the patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient])

- the patient is at significant risk of suicide (defined as answering "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS at any time during the study. Refer to Section 9.6.7.

A patient must be withdrawn from treatment if:

- the investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interest of the patient that he or she be withdrawn from treatment
- any site personnel break the randomization code for that patient
- the patient becomes pregnant
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing <2 weeks later
- the patient has a QT_{cF} interval >500 ms; the decision to withdraw the patient may be postponed until a repeat ECG is taken, if it is taken within 24 hours
- the patient experiences an anaphylactic reaction or another serious and/or severe hypersensitivity reaction to the eptinezumab infusion, as assessed by the investigator. If the event occurs during the infusion, the infusion must be discontinued immediately.

Patients who withdraw will not be replaced.

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

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

*If patient has been randomized in error and has not been administered IMP, the patient must be withdrawn. Withdrawal of patients randomized in error and who have received IMP should be based on a case-by-case evaluation of the individual risk/benefit. The decision about the administration of the second dose of IMP will be based on an individual risk/benefit assessment as judged by the investigator.

6 Investigational Medicinal Product (IMP)

6.1 Treatment Regimen

Patients will be randomly allocated via a centralized randomization system to one of two dosing sequences in accordance with the randomization list in a ratio of 1:1 and dosed according to Panel 4.

Panel 4 Dosing Schedule

Day/ End Week	A-B group	B-A group
Day 0/End week 0	400 mg eptinezumab	Placebo
Day 28/End week 4	Placebo	400 mg eptinezumab

The IMP will be administered at the Baseline Visit (Day 0/Visit 3) and at the end of Week 4 (Visit 6), by intravenous infusion over 45 minutes (+15 minutes)

6.2 IMP, Formulation, and Strength

The IMP supplied by Lundbeck in this study is:

- Eptinezumab 100 mg/ml (1ml/ vial) as Concentrate for Solution for Infusion.

400 mg eptinezumab will be dispensed as 4 vials of 100 mg/ml (1ml/ vial), Concentrate for Solution for Infusion. 4 x 1 ml. of 100 mg/ml Concentrate for Solution for Infusion is added to 100 mL of 0.9% normal saline, intravenously.

Placebo will be dispensed 100 mL of 0.9% normal saline, intravenously.

The pharmacist or designee responsible for receiving, storing, preparing, and dispensing eptinezumab and placebo IV infusions will be unblinded and will not be responsible for other aspects of the clinical study where blinding is necessary.

The IV bags containing eptinezumab + saline and IV bags containing saline only will be identical in appearance.

Doses will be administered intravenously over a period of 45 (+15) minutes by the blinded investigator or designee.

If the infusion is not completed or temporarily interrupted, the reason for the interruption must be recorded in the eCRF. If the investigator stops or pauses the infusion due to a potential safety or tolerability issue, an *Adverse Event* should be recorded.

Further instructions on preparation and procedures associated with administering the IV can be found in the *Pharmacy Manual and Infusion Guidelines*.

6.3 Manufacturing, Packaging, Labelling, and Storage of IMP

The IMP will be manufactured, packaged, labelled, released (by a qualified person [QP]), and distributed in accordance with the principles of *Good Manufacturing Practice*, under the responsibility of Lundbeck.

The IMP will be provided in a patient kit containing 4 single-use vials (as a concentrate for solution for infusion).

The wording on the labels will be in accordance with *Good Manufacturing Practice* regarding labelling and national and/or local regulatory requirements. If additional information is to be added when the IMP is dispensed to the patients, this will be clearly stated on the labels, and the investigator will be instructed to do so.

No manipulation, repackaging, or relabelling of IMP is permitted after QP release by Lundbeck, unless a repackaging/relabelling agreement exists, and the documentation is available to Clinical Supply, H. Lundbeck A/S, and, where necessary, new QP releases are made.

The IMP will be identified using a unique kit IMP number.

The IMP must be stored in a safe and secure location, and in accordance with the storage conditions specified on the label.

6.4 Method of Assigning Patients to Treatment

Interactive response technology (IRT) will be used in this study. Each patient will be assigned a screening number by the IRT, and that number will be used to identify the patient throughout the study. When a patient is to be randomized, the investigator uses the IRT. The IRT allocates the patient to a treatment during the call and assigns the patient a randomization number in accordance with the specifications from Biostatistics, H. Lundbeck A/S.

6.5 IMP Accountability

IMP accountability is documented in the IRT by the unblinded site staff and monitored by the unblinded CRA.

The investigator and the pharmacist must agree to only dispense IMP to patients enrolled in the study. The investigator or the pharmacist must maintain an adequate record of the receipt and distribution of the IMP. This record must be available for inspection at any time.

6.6 Unblinding Procedures

Pharmacovigilance, H. Lundbeck A/S, and the investigator or the pharmacist (if applicable), will have access to the unblinded information for the double-blind treatment for each patient. Access to these details will be via IRT.

The IRT unblinding procedure is described in the *IRT User Guide*.

The investigator may only break the code for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator should consult the CRA or CRO Medical Monitor before breaking the code. The investigator must record the date and reason for breaking the code on the *IMP Code Break Form* in the eCRF. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Form*. The CRA or CRO Medical Monitor must be notified immediately. The IRT will capture the date and time of the code break call. Information on the allocated

treatment will be provided during the call and by fax or email, depending on availability/preference. When the code is broken for a patient, the patient must be immediately withdrawn from the study. If this occurs during a visit, the investigator must complete the visit as a Withdrawal Visit; otherwise, the patient will be asked to attend a Withdrawal Visit.

7 Concomitant Medication

7.1 Concomitant Medication

Concomitant medication is any medication other than the IMP that is taken during the study from three months prior to Screening Visit 2 up until the Safety Follow-up Visit.

The concomitant medications that are disallowed or allowed with restrictions during the study are summarized in Appendix II.

Abortive therapy for cluster headache is allowed for the entire duration of the study (refer to list of therapies in Appendix II).

Some of the restrictions apply up until the end of the Placebo-controlled Period (Week 4) after which the patient can use transitional and preventive therapies for cluster headache.

Details of all cluster headache therapies (prescription and over-the-counter) taken within 12 months prior to Screening Visit 1 must be recorded in the eCRF at Screening Visit 1 and updated at Screening Visit 2, as / if applicable.

Details of all concomitant medication (prescription and over-the-counter) taken <3 months prior to Screening Visit 2 must be recorded in the eCRF at Screening Visit 2. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit.

For any concomitant medication for which the dose was increased due to worsening of a concurrent disorder after enrolment in the study, the worsening of the disorder must be recorded as an adverse event.

For any concomitant medication initiated due to a new disorder after enrolment in the study, the disorder must be recorded as an adverse event.

Use of Coronavirus Disease 2019 Vaccine

There is currently no data indicating that eptinezumab may interact with or impair the body´s immunological response to the COVID-19 vaccines. Hence, there are no indications for safety concerns of concomitant use of the COVID-19 vaccines with eptinezumab. As such, COVID 19 vaccination is allowed during the eptinezumab studies with the guidance measures as described below.

Patients must be allowed to receive their scheduled vaccination. If possible, a COVID-19 vaccine should not be administered within 1 week prior to Screening Visit 2 and until the Primary Outcome Visit (Week 2). Furthermore, if possible, a COVID-19 vaccine should not be administered within ±3 days of the second IMP infusion at Week 4. If the patient has recently received a COVID-19 vaccine, the investigator should judge if the patient can be administered the IMP infusion at the scheduled visit based upon the patient's individual response to the COVID-19 vaccine.

In the current study, if a patient is administered a COVID-19 vaccine (or any other prophylactic vaccine or other concomitant medication), this should be captured as concomitant medication in the eCRF, including the date that the vaccine was given. The name of the manufacturer and, if applicable, whether it was the "first" or "second" vaccination should also be added, in a bracket for example.

All adverse events, including those judged by the investigator to be related to the COVID-19 vaccine, must be captured in the eCRF on the *Adverse Event Form*. A causality assessment, including an alternative causality as relevant, must be provided on the *Adverse Event Form*.

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2. Further details are in section 9.

Screening Visit 1 is performed up to 52 weeks prior to Screening Visit 2. The patient will attend Screening Visit 2 as soon as they are at the beginning of a cluster headache bout, which is characterized by the presence of at least one typical cluster headache attack, and not later than 1 week after the start of the first attack. Under exceptional circumstances, when a patient is able to attend Screening Visit 2 only during the second week after the first typical cluster headache attack, the possibility to enrol this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient. After Screening Period 2, the patient will attend the Baseline Visit (Day 0/Visit 3), which is the first visit of the Placebo-Controlled Period (randomization and IMP infusion). All patients will continue in the Active Treatment Period of the study and will receive a second IMP infusion (eptinezumab 400 mg or placebo) at the end of Week 4 (Visit 6). The Safety Follow-up Visit will take place at Week 24 (Visit 10), 20 weeks (5 half-lives) after the second IMP administration.

The following visits will be site visits:

- Screening Visit 1
- Screening Visit 2
- Baseline Visit (Day 0/Visit 3) - randomization and IMP infusion
- Last Visit of the Placebo-controlled Period, at the end of Week 4 (Visit 6 - second IMP infusion)

- Completion Visit at Week 16 (Visit 9)
- Safety Follow-Up Visit at Week 24 (Visit 10)
- Withdrawal Visit (if applicable) - Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-Up Visit (SFU), scheduled 20 weeks (5 half-lives) after the last IMP administration.

All other study visits will be phone contact visits.

Patients will complete a daily eDiary from Screening Visit 2 until the Completion Visit (Week 16/Visit 9)/Withdrawal Visit. Patients will be given an eDiary at Screening Visit 2 and must be trained in its use and compliance requirements. Patients will complete electronic cluster headache diary entries daily. At each clinic visit and phone contact, a compliance check of the eDiary data will be conducted by site staff. In addition to the eDiary compliance checks performed at the defined clinic visits and phone contacts, ongoing evaluation of eDiary compliance will be performed by the sites (based on eDiary reporting) and more frequent contact with patients may be needed in case of non-compliance.

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

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

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

After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice.

8.2 Screening Visit 1

Signed informed consent must be in place before any study-related assessments are performed and may be obtained prior to Screening Visit 1.

Under exceptional circumstances, such as where COVID-19 pandemic restrictions impact the ability to perform site visits, the discussion with the patients about the *Informed Consent Form(s)* can be done as a virtual clinic visit and the *Informed Consent Form(s)* can be provided remotely in line with the US FDA and EMA guidances.[43, 44] According to the EMA guidance, this could comprise contacting the patients via phone or video-calls and obtaining oral consents, to be documented in the patients' medical records, supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the patients are back at the clinical sites.[44]

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

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

The site staff should maintain monthly phone contact with the patient during Screening Period 1 to ensure the patient is prepared to schedule Screening Visit 2 as soon as possible after experiencing a CH bout. These contacts should be documented in the source documentation.

Prior to the Screening Visit 2, an eligibility review will be managed by the CRO and a confirmation that the patient can continue further with the study procedures is required before Screening Visit 2.

For patients with a known history of episodic cluster headache as defined by IHS ICHD-3 classification,[1] who meet all inclusion criteria and do not meet any of the exclusion criteria relevant for Screening Visit 1, and who do not enter in a cluster headache bout by the end of the Screening Period 1, Screening Period 1 can be extended by an additional 6 months. The extension is granted on a case-by-case basis by the CRO Medical Monitor, after a confirmation of eligibility, based on Screening Visit 1 data in the eCRF.

Re-screening for Screening Visit 1 is allowed according to criteria outlined in 8.3.3.

For women of childbearing potential, the investigator must check current contraceptive methods. If relevant to do so, contraceptive therapy should be initiated if agreed by the patient and if there are no contraindications for the initiation of contraception.

8.3 Screening Visit 2

After Screening Visit 2 and prior to Baseline Visit (Day 0/Visit 3), an additional eligibility review managed will be by the CRO and confirmation that the patient can continue further with the study procedures is required before randomization.

In exceptional cases, the visit interval between Screening Visit 2 and the Baseline Visit (Day 0/Visit 3) may be extended with approval from the CRO Medical Monitor provided the CRO Medical Monitor accepts the rationale provided for the extension.

If a patient has insufficient number of attacks during Screening Period 2 to meet inclusion criterion 11, Screening Period 2 may be extended for an additional 7 days. See section 8.3.5 for further details.

Re-screening for Screening Visit 2 is allowed according to criteria outlined in 8.3.4.

At Screening Visit 2, the patient must be assisted with the provisioning and training of the eDiary and ePROs. Details will be provided in a separate user manual. See section 9.2.1.2 for further details on eDiary.

8.3.1 Pre-screening

Each site must record in a log which patients have been contacted and considered to attend Screening Visit 1.

8.3.2 Patient Identification Card

Each patient will be provided with a patient identification card that states, at a minimum, the name of the IMP, the study number, the patient identification number, the investigator's name, and an emergency telephone number providing 24-hour service.

The patient identification card should be returned to the investigator upon completion of the patient's participation in the study.

8.3.3 Re-Screening Visit 1

The Re-Screening Visit 1 must be conducted as a visit to the site. Re-screening of Screening Visit 1 is only allowed for patients with a Screening Visit 1 and who fail to meet one or more of the following selection criteria:

1. If a patient with a confirmed diagnosis of eCH as defined by IHS ICHD-3 classification[1] does not enter into a cluster headache bout during the maximum duration of Screening Period 1, including the potential 6-month extension of this period, granted by the CRO Medical Monitor. Refer to section 8.2.
2. If the diagnosis of eCH as defined by IHS ICHD-3 classification[1] cannot be confirmed due to disease duration of less than 12 months at the time of Screening Visit 1 (Inclusion criterion N°7).

3. If a female patient with a confirmed diagnosis of eCH as defined by IHS ICHD-3 classification becomes pregnant or is breastfeeding during Screening Period 1, the patient can repeat Screening Visit 1, if the study is still enrolling patients.
4. If a patient with a confirmed diagnosis of eCH as defined by IHS ICHD-3 classification[1] has been screen-failed on the amended eligibility criteria (Inclusion criteria 7 and 8 and Exclusion criterion 17). Re-screening of patients who have been previously screen-failed due the use of cannabinoids (either anamnesis or finding at Urine drug screen) must be approved by the CRO Medical Monitor, based on a confirmation from the investigator that the patient does not meet Exclusion criteria 10, 24 and 25.

At the new Screening Visit 1, the patient must sign new *Informed Consent Form(s)*. At the new Screening Visit 1, the patient will be assigned a new screening number. A patient re-screened for Screening Visit 1 must have a *complete* new Screening Visit 1, and all the eligibility criteria, relevant for Screening Visit 1 must be re-assessed at the new Screening Visit 1.

Authorization for re-screening of Screening Visit 1 may only be granted by CRO Medical Monitor after a thorough review of all data from the original Screening Visit 1.

The following information will also be recorded in the eCRF at the new Screening Visit 1:
- that the patient has previously been screened (Screening Visit 1) for the study
- that re-screening has been authorized by the CRO Medical Monitor
- the screening number that was assigned to the patient at the original Screening Visit 1

If a patient is re-screened, no data from the original Screening Visit 1 will be used.

A patient may only repeat Screening Visit 1 once.

8.3.4 Re-screening Visit 2

The Re-screening Visit 2 must be conducted as a visit to the site. Re-screening of Screening Visit 2 is only allowed for patients who fail to meet one or more of the following selection criteria:

1. If a patient with a previously documented history of cluster headache bout duration of at least 6 weeks enters, for any reason, Screening Period 2 too late and/or the investigator considers that there is a risk that the patient will have a spontaneous remission in less than 6 weeks after screening (Inclusion criterion N°10).
2. If a patient with a previously documented history of cluster headache bout duration of at least 6 weeks does not fulfil the required frequency of attacks (minimum of at least 7 total cluster headache attacks out of the 7-day Screening Period 2, including the extended Screening Period 2), the patient may be re-screened at the next bout.
3. If the patient does not fulfil Exclusion criterion N°17 (Disallowed medications or medications allowed with restrictions), refer to Appendix II:
   – The required duration of a washout period for a medication that is disallowed prior to screening, or,

  - A stable usage period for a medication that is allowed with restrictions prior to screening.

  The patient must already have either started the washout prior to screening or be on the allowed dosage as part of their standard clinical care. Washout or change in dosage may not be done specifically for inclusion into this study, but only if clinically indicated.
4. A patient has answered “yes” to either Question 4 or Question 5 on the “Suicidal Ideation” portion of the C–SSRS or answered “yes” to any of the suicide-related behaviors (Exclusion criterion N°23). Refer to Section 9.6.7. These screen-fail patients may be considered for re-screen if the following conditions are met:
   - The patient was referred to an appropriate mental health professional and received treatment.
   - At least 6 months has elapsed since the screen-fail.
   - The patient has not answered yes to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or answered "yes" to any of the suicide-related behaviors within the past 6 months, and are not considered by the investigator to be at significant risk for suicide.
5. Patients with uncontrolled high blood pressure at Screening Visit 2 (Exclusion criteria N°14 and 18): may be considered for re-screen once their blood pressure is controlled in the opinion of the investigator; any use of antihypertensive medication and dose must be stable for at least 2 months prior to Re-Screening Visit 2
6. Patients with a body mass index (BMI) ≥39 kg/m2 (Exclusion criterion N°19).
7. For patients affected by COVID-19, e.g. being in quarantine with a positive COVID-19 test with or without symptoms or other reasons related to COVID-19 which impacts the patients study participation, there will be an option of re-screening upon approval from the CRO MM.

Patients are not expected to have completed the full Screening Visit 2.

At the new Screening Visit 2, the patient must re-sign the *Informed Consent Form(s)*. The patient will use the screening number assigned at Screening Visit 1.

The following information will also be recorded in the eCRF at the new Screening Visit 2:
- that the patient has previously been screened (Screening Visit 2) for the study
- that re-screening has been authorized by the CRO Medical Monitor

Authorization for re-screening may only be granted by the CRO Medical Monitor after a thorough review of all available data from the original Screening Visit 2.

A patient may only repeat Screening Visit 2 once.

8.3.5 Extension of Screening Period 2

If the patient with a confirmed diagnosis of eCH as defined by IHS ICHD-3 classification[1], in a headache bout, does not meet the protocol requirement for minimum cluster headache activity (Inclusion criterion N°13) during Screening Period 2, based on the prospectively

collected data via the eDiary, Screening Period 2 may be extended for an additional 7 days. In these cases, the additional 7 days will begin on day 8. If the patient meets the required cluster headache activity by day 14 and the compliance requirements (6 out of 7 days compliance during days 8-14), the patient will continue in the study and the data from days 8-14 will be considered baseline data.

This is justified because the patient's cluster activity may escalate slowly resulting in an insufficient number of attacks during the first 7 days following the first cluster headache attack.

If the patient does not fulfil Exclusion criterion N°17 (Disallowed medications or medications allowed with restrictions, refer to Appendix II) and the investigator considers that the criterion can be met by allowing up to 7 additional days in the Screening Period 2 for washout. The possibility to enroll this patient in the study will be discussed with the investigator and the decision will be taken in the context of known history of typical duration of the bout for the individual patient.

Extension of Screening Period 2 with additional 7 days can be requested for other reasons (e.g. additional exams, consultations etc.).

Request for extension of the Screening Period 2 must be immediately notified and discussed with the CRO's medical monitor after a thorough review of all data from the Screening Visit 1 and 2.

8.4 Baseline Visit + IMP (Day 0/Visit 3)

The Baseline Visit (Day 0/Visit 3) also includes IMP administration and will occur 7 days after the Screening Visit 2. Inclusion and exclusion criteria review must be done prior to dosing at the Baseline Visit (Day 0/Visit 3).

Prior to the Baseline Visit (Day 0/Visit 3), study-specific eligibility must be reviewed by the CRO. A confirmation from the CRO Medical Monitor that the patient can continue further with the study procedures is required before randomization.

For procedures preceding and following IMP administration, see section 8.6.

8.5 Visit 6 + IMP

All patients will continue in the Active Treatment Period of the study and will receive at the end of Week 4 (Visit 6) a second IMP infusion as follows:

- Placebo - for patients who had received a first infusion with eptinezumab 400 mg at the Baseline Visit (Day 0/Visit 3)
- Eptinezumab 400 mg - for patients who had received a first infusion with Placebo at the Baseline Visit (Day 0/Visit 3)

For procedures preceding and following IMP administration, see section 8.6.

8.6 IMP Visits (Visits 3 and 6)

At IMP Visits, the patients will receive an IMP infusion. See section 6.1 and *Infusion Guidelines* for further instructions on procedures associated with administering the intravenous IMP.

Assessments involving interviews and scales must be administered at site before the infusion. ePROs will be completed in the clinic the following order; PGIC, SIS, EQ-5D-5L, HCRU, WPAI:GH2.0.

The eDiary and electronic patient-reported outcomes (ePROs) must be completed prior to infusion. A compliance check of eDiary data will be conducted by site staff and the patient must be assisted with re-training if necessary. In addition to the eDiary compliance checks performed at defined clinic visits and phone contacts, ongoing evaluation of eDiary compliance will be performed by the site (based on eDiary reporting) and more frequent contact with the patients may be needed in case of non-compliance. See section 9.2.1.2 for further details on eDiary.

Prior to IMP infusion:

- Patients must complete the ePROs. ePROs must be completed before pre-infusion blood sampling and urine sampling.
- The following assessments must be conducted: vital signs including body temperature, concomitant medications, AEs, physical and neurological examination (if done at the discretion of the investigator), ECG, blood sampling and urine sampling and C-SSRS administration.
- Vital signs must be assessed prior to blood sampling.

During IMP infusion: Infusion-related reactions (IRRs must be checked as part of the overall AE collection. IRRs must be assessed after the AE collection.

After end-of-IMP-infusion and before the patient is discharged from the site:

- Patients must be monitored for at least 1 hour.
- The following assessments must be conducted: vital signs including body temperature, IRRs and AEs. IRRs must be assessed after the AE collection. Vital signs must be assessed prior to blood sampling.
- A blood sample for eptinezumab quantification and exploratory biomarkers must be taken within approximately 1 hour after end-of-infusion.

Patients will be requested to stay longer should the investigator or designee determine this is clinically warranted. After the infusion, the patients will be under observation, but not confined to bed, unless the investigator decides, based on the patient's condition, that it is in the best interest of the patient to be confined to bed.

8.7 Phone Contacts (Visits 4, 5, 7, 8)

The patient will be contacted via phone for eDiary compliance checks to ensure that selected assessments have been completed and for collection of relevant information such as AEs and concomitant medication and C-SSRS (Week 8/Visit 7 only), which must be administered by the authorized rater at the site.

A compliance check of eDiary data will be conducted by site staff and the patient must be assisted with re-training if necessary. In addition to the eDiary compliance checks performed at the defined clinic visits and phone contacts, ongoing evaluation of eDiary compliance will be performed by the site (based on eDiary reporting) and more frequent contact with patients may be needed in the case of non-compliance. See section 9.2.1.2 for further details on eDiary.

Additionally, the following ePROs must be completed in the remote setting in alignment with the scheduled phone contacts (see Panel 2): PGIC (Visit 4, 5 and 7), SIS (Visit 5), EQ-5D-5L (Visit 5 and 7). During the Placebo-controlled Period, ePROs which are scheduled in alignment with a phone contact must be completed in the remote setting on the day the scheduled phone contact date. During the Active Treatment Period, ePROs which are scheduled in alignment with a phone contact must be completed in the remote setting and can be completed on the day or within 1 day prior to the scheduled phone contact date.

Only site staff trained and listed in the delegation log will conduct phone contacts and hence be allowed to call the patient. Each phone contact must be documented in medical notes and used for source data verification when completing the eCRF and for subsequent monitoring.

Phone contacts should be planned to maintain the visit schedule relative to the Baseline Visit (Day 0/Visit 3).

8.8 Completion Visit (Visit 9)

At the Completion Visit, the patient must be assisted with the closeout of the eDiary.

8.9 Withdrawal Visit

Patients who withdraw from the study prior to the Completion Visit (Week 16/Visit 9) will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal.

No new information will be collected from patients who withdraw from the study, except information collected in relation to the scheduled Withdrawal Visit and Safety Follow-Up Visit or needed for the follow-up of adverse events (section 10.5).

The reason for withdrawal must be recorded in the eCRF.

For a patient who withdraws consent:

- if the patient withdraws consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including that visit will be used
- if the patient withdraws consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including that visit will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical records
- if the patient explicitly requests that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected

8.10 Safety Follow-up Visit (Visit 10)

The Safety Follow-Up Visit must be conducted as a visit to the site. The Safety Follow-Up Visit (SFU), should be scheduled 20 weeks (5 half-lives) after the last IMP administration.

A safety follow-up is conducted to capture adverse events that occur after the Completion/Withdrawal visit, as well as to follow up on the outcome of adverse events ongoing at the Completion/Withdrawal Visit.

Patients who withdraw from the study, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-Up Visit at 20 weeks (5 half-lives) after the last administration of IMP.

For adverse events that were ongoing at the Completion/Withdrawal Visit and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still ongoing at the safety follow-up, the *Ongoing Adverse Event* checkbox on the Adverse Event Form must be ticked. SAEs must be followed until resolution or the outcome is known.

The safety follow-up for patients who withdraw consent must be performed, if at all possible; any information collected will be recorded in the patients' medical records.

8.11 Unscheduled Visit

Unscheduled visits can be completed if required as either site visit or telephone visits. At these visits, clinical safety laboratory tests, ECG, vital signs, physical examination, neurological examination, C-SSRS, body measurement, mental health consultation information or pregnancy tests can be performed. In case of any additional tests performed not covered by the existing tests specified in the protocol and the eCRF, the results can be reported in connection with an AE reporting (see section 10) or documented in the medical records, as applicable.

8.12 End-of-study Definition

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

9 Assessments

9.1 Screening and Baseline Procedures and Assessments

9.1.1 Demographics and Baseline Characteristics

Prior to enrolling a patient in the study, the investigator must ascertain that the patient meets the selection criteria. Refer to section 5.3.

The following assessments will be performed after the *Informed Consent Form(s)* have been signed at Screening Visit 1:

- Demographics (age, sex, race). Race will not be collected if restricted per local regulations.
- Prior episodic cluster headache documented history for review and documentation of previous treatment for episodic cluster headache within 12 months prior to Screening Visit 1 (see section 12 for definition of adequately documented records)
- Other recent medication
- Relevant history (social, medical, psychiatric, neurological)
- Substance use (e.g., smoking and alcohol consumption)
- Height
- Family history of cluster headache
- Urine Pregnancy test
- Vital signs (including body temperature), weight

The following assessments will be performed Screening Visit 2:

- Re-sign *Informed Consent Form(s)* signed at the Screening Visit 1
- Prior episodic cluster headache documented history for review and documentation of previous treatment for episodic cluster headache within 12 months prior to Screening Visit 1 (see section 12 for definition of adequately documented records)
- Other recent medication
- Relevant history (social, medical, psychiatric, neurological)
- Substance use (e.g., smoking and alcohol consumption)
- Signs and symptoms present at Screening Visit 2 and/or baseline (before IMP administration)
- Serum Pregnancy test
- Blood and urine samples for clinical safety laboratory tests
- Urine drug screen
- Vital signs (including body temperature), weight, ECGs

- Examinations (physical, neurological)
- C-SSRS
- eDiary/ePRO training
- eDiary recording

9.1.2 Diagnostic Assessments

IHS ICHD-3 guidelines[1] sections 3.1 and 3.1.1 for episodic cluster headache are the diagnostic criteria to be used when assessing patient eligibility. Fulfilment of criteria for episodic cluster headache according to the inclusion criteria in this protocol will be confirmed via prospectively collected information in the eDiary during Screening Period 2 (i.e., minimum 7 and maximum of 56 CH attacks for the 7-day Screening Period 2). The lower and the upper limit for CH attack frequency is in line with the IHS ICHD-3 criteria for CH.

Definition of an eDiary Compliant Day: A Compliant Day is defined as any day where either:

- a headache event is reported
- or evening diary is completed confirming patient did not have any new headache to report

Prior to enrolment, the investigator will review the data in the eDiary Eligibility Report to determine if eligibility criteria are fulfilled.

Panel 5 IHS ICHD-3 guidelines[1] for Episodic Cluster Headache

3.1 Cluster Headache

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
C. Either or both of the following:
   (1) at least one of the following symptoms or signs, ipsilateral to the headache:
      a. conjunctival injection and/or lacrimation
      b. nasal congestion and/or rhinorrhoea
      c. eyelid oedema
      d. forehead and facial sweating
      e. miosis and/or ptosis
   (2) a sense of restlessness or agitation
D. Occurring with a frequency between one every other day and eight per day
E. Not better accounted for by another ICHD-3 diagnosis.

3.1.1 Episodic cluster headache

A. Attacks fulfilling criteria for 3.1 Cluster headache and occurring in bouts (cluster periods)
B. At least two cluster periods lasting from seven days to one year (when untreated) and separated by pain-free remission periods of ≥3 months.

In episodic cluster headache, during the cluster periods (bouts), the attacks occur in series lasting for weeks or months. Cluster periods usually last between two weeks and three months and are separated by remission periods usually lasting months (at least three months) or years.[1]

9.1.3 Drug and Alcohol Screen

A urine drug screen will be performed at the central laboratory for Screening Visit 2 only. A positive result must be discussed with the CRO Medical Monitor and will be evaluated in the context of concomitant medication use and exclusion criterion 10.

9.2 Efficacy Assessments

Efficacy assessments include the eDiary to record daily cluster headache data and ePROs (PGIC, SIS).

Patients will record eDiary cluster headache data on a daily basis from the Screening Visit 2 until the Completion Visit (Week 16/Visit 9).

Patients will complete the PGIC and SIS along with the pharmacoeconomic assessment ePROs (see section 9.3). The ePROs should preferably be completed in the following order; PGIC, SIS, EQ-5D-5L, HCRU, WPAI:GH2.0. It is preferable that the same order of assessments is used per patient and the scheduled time of the day for the assessments is as consistent as possible across all the study visits.

ePROs will be completed in alignment with clinic visits and phone contacts (see Panel 2):

- *ePROs which are scheduled in alignment with a clinic visit:*
  - During the Placebo-controlled Period - must be completed in the clinic;
  - During the Active Treatment Period and Post-treatment Observational Period can be completed in the clinic or in the remote setting within 1 day prior to the scheduled clinic visit date. On the day of the Baseline Visit (Day 0/Visit 3), patients must complete the ePROs prior to infusion.
- *ePROs which are scheduled in alignment with a phone contact*:
  - During the Placebo-controlled Period - must be completed in the remote setting on the day of the scheduled phone contact date;
  - During the Active Treatment Period and Post-treatment Observational Period must be completed in the remote setting and can be completed on the day or within 1 day prior to the scheduled phone contact date.
- HCRU and WPAI:GH2.0 must be administered at the site.

9.2.1 Clinical Outcome Assessments (COAs)

9.2.1.1 Use of COA Tools

The COA tools are the eDiary and ePROs, guidance to patients on how to complete the tools will be given by designated staff (see section 9.2.1.6). Detailed instructions will be provided in a separate *eDiary* and e*PRO Training Module.*

The COA tools will be administered in the local language. Only those provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study.

The following COA tools will be used for efficacy assessments:

- eDiary – to assess the number of daily cluster headache attacks, pain severity and medication use (i.e., the start and stop dates of cluster headache attacks, and use of acute eCH medications).
- PGIC - to assess overall change in the severity of illness following treatment.
- SIS – to assess quality of life resulting from insomnia as caused by cluster headache attacks

9.2.1.2 eDiary

At Screening Visit 2, the patient must be assisted with the provisioning of the eDiary and must be trained in eDiary use and compliance requirements by designated site staff. Patients will be instructed to complete the eDiary on a daily basis, from Screening Visit 2 until the Completion Visit (Week 16/Visit 9). During the Completion Visit (Week 16/Visit 9) or the Withdrawal Visit (for patients who withdraw), eDiary close-out must be performed while the patient is on site. Details will be provided in a separate *eDiary Training Module.*

The content of the cluster headache diary is developed on key characteristics as mentioned in the definition of episodic cluster headache (see section 9.1.2). The eDiary consists of applications and reports which will be used to derive the cluster headache endpoints. For each day, the patient should record if they experienced any cluster headache attacks. For each experienced cluster headache attack, the start date and time will be collected. The patient will record further daily information regarding cluster headache characteristics and intake of cluster headache acute medication. Cluster headache items will be assessed with a yes/no response; and severity will be rated on an ordinal scale ranging from 0-4 (headache pain ratings: 0=none/barely any pain; 1=mild; 2= moderate; 3= severe; 4=excruciating).[46] Additional details regarding the questions that patients will answer can be found in the *eDiary Training Module*.

Screening Visit 2 will correspond to the day of eDiary distribution and will start the 7-day eDiary Screening Period 2. Any patient found to be ineligible for the study during Screening Period 2 will not be randomized. An *eDiary Eligibility Report* will be used to review baseline cluster headache attack days and eDiary compliance during the 7-day Screening Period 2 for the eligibility assessment of:

- a minimum of at least 7 total cluster headache attacks out of the 7-day period
- a maximum of 56 cluster headache attacks out of the 7-day period
- compliance by entry of cluster headache data for at least 6 out of the 7 days of Screening Period 2

On the Baseline Visit (Day 0/Visit 3), patients must ensure to complete eDiary recording of cluster headache attacks that ended prior to infusion (i.e., for cluster headaches attacks which are ongoing or not yet recorded in the eDiary).

On each day during the study until the Completion Visit (Week 16/Visit 9)/Withdrawal Visit, the patient will be asked to record eDiary data for the day.

Clinical study site staff will be given access to the eDiary data. Compliance data (based on eDiary reporting) will be made available throughout the study to site staff for review on a regular basis. At least 6 out of 7 days per week compliance is needed during Screening Period 2. At each clinic visit and phone contact, a compliance check of eDiary will be conducted by site staff. Additionally, ongoing evaluation of eDiary compliance will be performed by the site and more frequent contact with patients may be needed in case of non-compliance. All follow-up with patients regarding eDiary compliance should be documented in the source records.

9.2.1.3 Patient Global Impression of Change (PGIC)

The PGIC is a single patient-reported item reflecting the patient's impression of change in their disease status since the Baseline Visit (Day 0/Visit 3) (that is, in relation to activity limitations, symptoms, emotions, and overall quality of life). The item is rated on a 7-point scale, where a high score indicate improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse). It takes approximate 1 minute to complete the scale.

9.2.1.4 Sleep Impact Scale (SIS)

The SIS[47] is a patient-reported scale to assess quality of life resulting from sleep disturbance. The SIS questionnaire includes 35 items belonging to 7 domains to assess sleep impact: daily activities (5 items); emotional well-being (4 items); emotional impact (4 items); energy/fatigue (5 items); social well-being (6 items); mental fatigue (3 items); and satisfaction with sleep (8 items). Each item, for 6 out of the 7 domains, is rated on a 5-point scale ranging from 1 ("always" or "all of the time") to 5 ("never" or "none of the time"), whereas satisfaction with sleep is rated on a 5-point scale ranging from 1 (very satisfied) to 5 (very dissatisfied). Each domain yields a score ranging from 0-100. A higher score indicated better quality of life (reverse scoring for the satisfaction with sleep domain). It takes approximately 10 minutes to complete the SIS.

9.2.1.5 External COA Monitoring Oversight

Lundbeck reserves the right to use external quality oversight to ensure eDiary compliance and data quality, as well as ensure accurate completion of COAs. For this study, the CRO will conduct the external data monitoring (to be agreed with Lundbeck).

9.2.1.6 COA Tool Training

The COA tools are patient-reported. Therefore, designated site staff will receive guidance on good standards in completion of the COAs, in order to adequately train patients on completion of the eDiary and ePROs.

COA training will be conducted by the CRO (as agreed with Lundbeck). Site staff will complete their designated training curriculum based on their initial qualification status and assigned role. Any exceptions must be discussed and approved by Lundbeck and/or its designee. The training program will also include general COA quality assurance and management guidance.

Only site staff who have adequate experience with cluster headache and who have received adequate training on good standards in completion of the eDiary and ePROs will be authorized to train the patients on completion of the eDiary and ePROs in the study.

Documentation of training will be provided to site staff for archiving in the investigator trial master file (TMF).

New eDiary and ePRO trainers joining the study must be trained similarly.

9.3 Pharmacoeconomic Assessments

Pharmacoeconomic assessments include ePROs (EQ-5D-5L, HCRU, WPAI:GH2.0).

Patients will complete these ePROs along with the efficacy assessment ePROs (PGIC and SIS, see sections 9.2.1.3 and 9.2.1.4). The ePROs should preferably be completed in the following order; EQ-5D-5L, HCRU, WPAI:GH2.0). It is preferable that the same order of assessments is used per patient and the scheduled time of the day for the assessments is as consistent as possible across all the study visits.

ePROs will be completed in alignment with clinic visits and phone contacts:

- *ePROs which are scheduled in alignment with a clinic visit* (see Panel 2):
  - During the Placebo-controlled Period - must be completed in the clinic;
  - During the Active Treatment Period and Post-treatment Observational Period can be completed in the clinic or in the remote setting within 1 day prior to the scheduled clinic visit date. On the day of the Baseline Visit (Day 0/Visit 3), patients must complete the ePROs prior to infusion.

- *ePROs which are scheduled in alignment with a phone contact* (see Panel 2):
  - During the Placebo-controlled Period - must be completed in the remote setting on the day of the scheduled phone contact date;
  - During the Active Treatment Period and Post-treatment Observational Period must be completed in the remote setting and can be completed on the day or within 1 day prior to the scheduled phone contact date.
- HCRU and WPAI:GH2.0 must be administered at the site.

9.3.1 Clinical Outcome Assessments (COAs)

9.3.1.1 Use of COA Tools

Refer to section 9.2.1.1 for further information on use of COA tools.

The following COA tools will be used for pharmacoeconomic assessments:

- EQ-5D-5L - to assess the overall state of health
- HCRU - to assess cluster headache-specific healthcare resource utilization
- WPAI:GH2.0 - to assess overall effect of health on productivity at work and daily activities

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

The EQ-5D-5L[48] is a patient-reported assessment designed to measure the patient's wellbeing. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS ranges from 0 (*worst imaginable health state*) to 100 (*best imaginable health state*). It takes approximately 5 minutes to complete the EQ-5D-5L.

9.3.1.3 Health Care Resource Utilization (HCRU)

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

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

The WPAI:GH2.0[49] is a patient self-rated scale designed to provide a quantitative measure of the work productivity and activity impairment due to a health condition. The WPAI:GH2.0 assess activities over the preceding 7 days and consists of 6 items: 1 item assess employment (yes/no); 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. It takes approximately 5 minutes to complete the WPAI:GH2.0.

9.3.1.5 External COA Monitoring Oversight

See section 9.2.1.5.

9.3.1.6 COA Training

See section 9.2.1.6.

9.4 Pharmacokinetic Assessments

9.4.1 Blood sampling for eptinezumab quantification

The blood samples (maximum total volume: 12 mL per patient) for eptinezumab quantification in plasma will be drawn in accordance with Panel 2. The samples will be analysed for free eptinezumab using a validated bioanalytical method by a bioanalytical laboratory under the responsibility of Sponsor. The bioanalytical method will be defined in a bioanalytical protocol and be reported in a bioanalytical report.

The results will be reported separately.

9.5 Pharmacodynamic Assessments

9.5.1 Pharmacodynamic/Exploratory Biomarkers

Blood samples (maximum total volume 24 mL) for the pharmacodynamic/exploratory biomarker assessment of the CGRP and eptinezumab-CGRP complex will be collected in accordance with Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The results from these analyses will be reported separately.

9.6 Safety Assessments

9.6.1 Adverse Events

The patients will be asked a non-leading question (for example, “How do you feel?”, “How have you felt since your last visit?”) at each visit, starting at Screening Visit 2. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of each adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See section 10 for further information on adverse events.

9.6.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 6.

Panel 6 Clinical Safety Laboratory Tests

Haematology	**Liver**[b]	**Immune response lab kit**[h]
B-haemoglobin [HGB] B-erythrocyte count [RBC] B-total leucocyte count [WBC] B-neutrophils[a] [NEUTLE] B-eosinophils[a] [EOSLE] B-basophils[a] [BASOLE] B-lymphocytes[a] [LYMLE] B-monocytes[a] [MONOLE] B-thrombocyte count [PLAT] B-haematocrit [HCT] P-prothrombin time [PT]	S-total bilirubin [BILI] S-conjugated bilirubin [BILDIR] S-alkaline phosphatase [ALP] S-alanine aminotransferase [ALT] S-aspartate aminotransferase [AST] S-gamma-glutamyl transferase [GGT]	P-histamine [HISTAMINE] S-tryptase [TRYPTASE] immunoglobulin E [IgE] complement C3, C4 [C3 and C4]
		Infection[c] S-C-reactive protein [CRP]
Electrolytes[b]	**Kidney**[b]	**Urine**[g]
S-sodium [SODIUM] S-potassium [K] S-calcium (total) [CA]	S-creatinine [CREAT] S-urea nitrogen [UREAN]	U-protein (dipstick) [PROT] U-glucose (dipstick) [GLUC] U-blood (dipstick) [OCCBLD] Urine drug screen
Endocrine and Metabolic[b]	**Lipids**[b,d]	**Pregnancy**[e]
S-albumin [ALB] S-glucose[d] [GLUC] B-HbA1c [HBA1C] S-creatine phosphokinase [CK]	S-low density lipoprotein [LDL] S-high density lipoprotein [HDL] S-triglycerides [TRIG] S-cholesterol (total) [CHOL]	S-hCG[f] [HCG] Urine (dipstick)
B = blood; P = plasma; S = serum; U = urine		

a Count and % of total leucocytes
b Clinical chemistry
c Performed at Screening Visit 2 only
d Fasting, when possible
e Only for women of childbearing potential
f Performed at Screening Visit 2 and Safety Follow-Up Visit only
g If urine dipstick is positive, a urine microscopic panel will be conducted
h Performed per investigator judgement, see section 10.1.3

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2.

The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual.*

It is mandatory for blood and urine samples to be analysed by the central laboratory. If necessary, for logistical reasons and per the investigator's discretion, a local laboratory may also be used at Screening Visit 2. Central laboratory results supersede local laboratory results. If central laboratory results are not available for the eligibility assessment, the local laboratory results may be used to confirm eligibility.

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator as "not clinically significant" or "clinically significant" with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be

repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilized or until the value has returned to a clinically acceptable value (regardless of relationship to the IMP). A patient with a value that is out-of-range at the Completion Visit (Week 16/Visit 9) or Withdrawal Visit and considered clinically significant must be followed in accordance with usual clinical practice. If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical records.

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*, starting from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

The central laboratory will be notified by Lundbeck when the biological samples may be destroyed.

9.6.3 Vital Signs

The investigator may appoint a designee (for example, nurse or paramedic) to measure vital signs, provided this is permitted according to local regulations and provided the investigator has trained the designee how to measure vital signs. The investigator must take responsibility for reviewing the findings.

Pulse rate and blood pressure will be measured using a standard digital meter. Pulse rate and blood pressure will be measured in the following order: supine, sitting, and standing after the patient has rested in each position for at least 3 minutes.

At IMP visits, vital signs including body temperature is assessed both prior to and after infusion. When coinciding, vital signs including body temperature must be assessed prior to blood sampling.

Any out-of-range vital sign considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form,* starting from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

9.6.4 Height and Weight

The patient's height will be measured once at Screening Visit 1.

The patients will be weighed wearing light clothing and no shoes. A similar amount of clothing must be worn on each occasion.

Any weight change considered clinically significant by the investigator must be recorded as an adverse event on an Adverse Event Form, starting from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

9.6.5 Electrocardiograms (ECGs)

A standard 12-lead ECG will be recorded using digital ECG recording equipment provided to the investigator or, upon agreement, to an external cardiology centre. The ECGs will be transferred digitally to a central ECG laboratory for evaluation. The investigator will be provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory.

The results from the central ECG laboratory will include the PR, QRS, QT, and QTc intervals.

The investigator has the final decision on the interpretation of the ECG results. Any abnormal ECG result or out-of-range ECG parameter value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*, starting from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

9.6.6 Physical and Neurological Examinations

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

The investigator may appoint a designee to be primarily responsible for performing the physical and neurological examinations, such as physician assistant or nurse practitioner (as applicable) provided this is permitted according to local regulations. The investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all the physical examinations.

The physical examination must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen (including the renal regions) and musculoskeletal system.

Any abnormal finding or out-of-range value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*, starting from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2.

9.6.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study.[50] The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of ideation, and 4 questions addressing suicidal behaviour. For this study, the following versions of the

scale are used: the “Baseline/Screening” version (lifetime and 1-month assessment) and the “Since last visit” version (for all subsequent visits). It takes approximately 5 minutes to administer and rate the C-SSRS.

The C-SSRS must be administered in the local language.

The C-SSRS should only be administered by a qualified rater. For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study. Any exceptions must be discussed and approved by Lundbeck and/or its designee.

Rater training and certification will be conducted by the CRO as agreed with Lundbeck. Raters will complete their designated training curriculum based on their initial qualification status and assigned role. Only raters who qualify on study specific Rater Certification Programme will be authorized to administer the C-SSRS in the study. Documentation of training and certification will be provided to raters for archiving in the investigator trial master file (TMF). No patient must be rated before the documentation has been archived. New raters joining the study must be trained and certified by using the same certification process. Detailed instructions on how to administer the C-SSRS will be provided to the site in a *C-SSRS Guideline*.

In case the C-SSRS assessment indicates elevated acute suicide risk (the patient answering: "yes" to suicidal ideation questions 4 or 5 or answering: "yes" to suicidal behaviour at any time during the study, it is the responsibility of the investigator to withdraw the patient from further treatment and to promptly refer the patient to an appropriate mental health care professional for a psychiatric evaluation.

Any finding on the C-SSRS that is considered clinically significant by the investigator should be reported as an AE.

9.6.8 Anti-Drug Antibody (ADA) including Neutralizing Antibody (Nab) Assessments

Blood samples for ADA, including NAb assessments (maximum total volume 7.5 mL), will be collected in accordance with Panel 2. The samples will be analysed using validated methods by an analytical laboratory under the responsibility of Sponsor. The analytical methods will be defined in analytical protocols and be reported in analytical reports.

9.7 Biobanking

9.7.1 General Considerations

This study includes collection of blood samples for long term storage and use in a possible future explorative biomarker research study, that may help to increase our understanding of the aetiology of psychiatric or neurological diseases, such as migraine and the molecular basis of the drug response.

Although the potential future exploratory biomarker analyses will help to increase our understanding of the aetiology of episodic cluster headache and the molecular basis of the drug response, the efforts described in this protocol are strictly research based. Therefore, as the complex interactions between genes, biomarkers and disease are currently not characterized to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses will as per usual not be given to either the study participants or the investigator. For the same reasons, individual results will not be added to the patients' medical records.

The patients will have no direct benefit from the exploratory biomarker analyses.

To ensure privacy protection, the blood samples for RNA gene expression profiling, proteomics/metabolomics analysis and future ADA assessments will be single-coded using the patient's screening number. The blood samples for the pharmacogenetic (DNA) biomarker analysis will be double-coded, i.e. one code key will be stored at the site and the other at Lundbeck. To link a DNA sample to a specific subject, both code keys are needed.

The blood samples collected for the possible future exploratory biomarker analysis may be shared with academic and public institutions and other companies. However, Lundbeck will retain full control of the samples and their use in accordance with the information in the Patient Information Sheet and a *Material Transfer Agreement*. Furthermore, the results based on the analysis of the samples may be pooled across studies to increase the statistical power of the analyses.

9.7.2 Blood Sampling for Gene Expression Profiling

Blood samples for gene expression profiling will be collected in two PAXgene RNA tubes (2.5 mL) or equivalent in accordance with Panel 2. The maximum volume of blood to be collected during the study for this purpose will be 15 mL.

Samples for gene expression profiling will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by CRO or by a bona fide research collaborator.

9.7.3 Blood Sampling for Metabolomics and/or Proteomics

Blood samples for plasma separation and metabolomics and/or proteomics will be collected in one 10 mL K2 EDTA tube or equivalent in accordance with Panel 2. The maximum volume of blood to be collected during the study for this purpose will be 30 mL.

Samples for gene expression profiling will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by CRO or by a bona fide research collaborator.

9.7.4 Blood Sampling for Pharmacogenetics

It is optional for the patient to donate a blood sample for exploratory pharmacogenetic analysis.

Blood samples for subsequent DNA extraction and aliquoting will be collected in 9 mL K3 EDTA tube or equivalent in accordance with Panel 2. The maximum volume of blood to be collected during the study for this purpose will be 9 mL.

The extracted DNA aliquots will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by CRO or by a bona fide research collaborator.

The genetic variants to be analysed may include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). The analytical methods may be polymerase chain reaction (PCR), quantitative PCR (qPCR), sequencing, or whole genome scans on microarrays.

9.7.5 Blood sampling for possible future anti-drug antibody assessments

Whole blood samples for serum separation and potential future anti-eptinezumab antibody analyses will be collected in 2.5 mL silica clot activator (SST) tube or equivalent in accordance with Panel 2.

The maximum volume of blood to be collected during the study for this purpose will be 7.5 mL.

The samples for future anti-drug antibody assessments will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by CRO or by a bona fide research collaborator.

9.7.6 Blood Sampling for Future Exploratory Biomarkers

Blood sample for plasma separation and explorative biomarkers assessment will be collected in one 4 mL K2 EDTA tube or equivalent in accordance with Panel 2.

The blood sampling and handling procedures are described in the Study Operations Manual. The maximum volume of blood to be collected during the study for this purpose will be 20 mL.

The plasma samples will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by CRO or by a bona fide research collaborator. The samples and any derived material will be destroyed ≤10 years after the end of the study (as defined in section 9.4).

9.8 Order of Assessments

At the Baseline Visit (Day 0/Visit 3), **prior** to IMP infusion:

- After randomization, patients must complete the ePROs. ePROs must be completed before the pre-infusion blood sampling and urine sampling.
- The following assessments must be conducted: vital signs including body temperature, concomitant medications, AEs, physical and neurological examination (if done at the discretion of the investigator), ECG, blood sampling and urine sampling and C-SSRS administration.
- Vital signs must be assessed prior to blood sampling.

At the Baseline Visit (Day 0/Visit 3), **during** IMP infusion: IRRs must be checked as part of the overall AE collection. IRRs must be assessed after the AE collection.

At the Baseline Visit (Day 0/Visit 3), **After** end-of-IMP-infusion and before the patient is discharged from the site:

- Patients must be monitored for at least 1 hour.
- The following assessments must be conducted: vital signs including body temperature, IRRs and AEs. IRRs must be assessed after the AE collection. Vital signs must be assessed prior to blood sampling.
- A blood sample for eptinezumab quantification and exploratory biomarkers must be taken within approximately 1 hour after end-of-infusion.

ePROs:

- *ePROs which are scheduled in alignment with a clinic visit:*
  - During the Placebo-controlled Period - must be completed in the clinic;
  - During the Active Treatment Period and Post-treatment Observational Period can be completed in the clinic or in the remote setting within 1 day prior to the scheduled clinic visit date. On the day of the Baseline Visit (Day 0/Visit 3), patients must complete the ePROs prior to infusion.
- *ePROs which are scheduled in alignment with a phone contact*:
  - During the Placebo-controlled Period - must be completed in the remote setting on the day of the scheduled phone contact date;
  - During the Active Treatment Period and Post-treatment Observational Period must be completed in the remote setting and can be completed on the day or within 1 day prior to the scheduled phone contact date.
- HCRU and WPAI:GH2.0 must be administered at the site.
- ePROs should preferably be completed in the following order; PGIC, SIS, EQ-5D-5L, HCRU, WPAI:GH2.0. It is preferable that the same order of assessments is used per patient and the scheduled time of the day for the assessments is as consistent as possible across all the study visits.

9.9 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 200 mL during the study.

Additional blood samples may be required if the original blood samples are not viable or if re-testing is required.

The biobank blood samples and any derived material for potential future exploratory gene expression profiling, metabolic or proteomic biomarker analyses or anti-drug antibody assessments will be destroyed ≤10 years after the end of the study (see definition in section 8.11).

The biobank blood samples and any derived material for potential future exploratory pharmacogenetic analyses will be destroyed ≤15 years after the end of the study (see definition in section 8.11).

Samples for eptinezumab quantification, exploratory biomarkers and anti-drug antibody assessments will be retained for up to 5 years after reporting of the study (see section 17.2).

9.10 Treatment Compliance

Responsible study personnel will administer the infusions of IMP. Treatment compliance verification should be documented in the patient's source documents and study specific IMP documents and verified by a CRA during monitoring.

Anyone administering the IMP to the patient must be listed in the delegation log.

The information from the IMP Administration Form must be entered in the eCRF.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[51]

Adverse event – is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

A worsening of a pre-existing or chronic condition is considered an adverse event and must be reported as such. Medical conditions, which existed prior to the time of informed consent into the clinical study are part of the patient's medical history and are not considered an adverse event. Unchanged, chronic, non-worsening or pre-existing conditions from the time of informed consent are not adverse events and should not be reported as such.

Adverse events (serious and non-serious) must be collected, recorded, and reported to Lundbeck from the time the patient has signed/re-signed the informed consent form(s) at Screening Visit 2. Any event (serious or non-serious) that are reported to the investigator prior to Screening Visit 2 should be considered and recorded as medical history.

Serious adverse event (SAE) – is any adverse event that:

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the *Informed Consent Form* and that did not change in intensity are not adverse events. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE.

If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Suspected unexpected serious adverse reaction (SUSAR) – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure,*[24] and related to a medicinal product by either the investigator or Lundbeck.

Overdose – is a dose administered to the patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

The investigator must assess the *intensity* of the adverse event using the following definitions, and record it on the *Adverse Event Form*:

- *Mild* – the adverse event causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.
- *Moderate* – the adverse event is sufficiently uncomfortable to produce some impairment of the patient's normal activities.
- *Severe* – the adverse event is incapacitating, preventing the patient from participating in the patient's normal activities.

Assessment of Causal Relationship

The investigator must assess the *causal relationship* between the adverse event and the IMP using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Probable* – the adverse event has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
- *Possible* – the adverse event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
- *Not related* – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent disorder or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

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

For pre-treatment adverse events, a causality assessment is not relevant.

Assessment of Outcome

The investigator must assess the *outcome* of the adverse event using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Recovered* – the patient has recovered completely, and no symptoms remain.
- *Recovering* – the patient's condition is improving, but symptoms still remain.
- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

10.1.3 Management of Reactions to Study Drug

There are no specific antidotes to an infusion of eptinezumab.

A medical emergency should be treated appropriately by the investigator using proper standard of care, according to their typical clinical practice and local guidelines for that emergency condition.

Should a medical condition arise that the investigator believes is related to the study drug, clinical judgment should be used to provide the appropriate response including the consideration of discontinuation of study drug. If a patient experiences an anaphylactic reaction or another severe and/or serious hypersensitivity reaction during the IMP infusion, as assessed by the investigator, the infusion must be discontinued immediately (see section 5.4) and appropriate therapy instituted. Any events believed to be allergic reactions should be discussed with the medical monitor.

The site will have the possibility to collect, at the time of the event, additional blood specimens using the immune response lab kit, per the laboratory manual. This assessment includes plasma histamine, serum tryptase, immunoglobulin E, and complement components.

10.2 Pregnancy

Although not necessarily considered an adverse event, a pregnancy in a patient in the study must be recorded on an *Adverse Event Form*, as well as on a *Pregnancy Form* (paper), even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be reported as an SAE; hospitalization for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion must be indicated on the *Serious Adverse Event Form*. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

The investigator must follow up on the *outcome* of the pregnancy and report it on a *Pregnancy Form* (paper). The follow-up must include information on the neonate at least up until the age of 1 month.

If required by local regulations, the patient and her partner will be asked to sign a separate *Informed Consent Form* in case of pregnancy.

10.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events) must be recorded on an *Adverse Event Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours or occur at the day of the IMP administration);

intensity; causal relationship to the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded, if available. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Form* and report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (see section 10.4).

If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported and linked to the previously reported adverse events.

10.4 Reporting Serious Adverse Events (SAEs)

The investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing a *Serious Adverse Event Form*.

The initial *Serious Adverse Event Form* must contain as much information as possible and, if more information about the patient's condition becomes available, the *Serious Adverse Event Form* must be updated with the additional information.

If the investigator cannot report the SAE in Rave®, then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to:

Fax: +45 36 30 99 67
email: ICSRquery@lundbeck.com

If sent by email, the investigator must ensure that the SAE fallback form is sent password protected and that the password is sent in a separate email.

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local requirements.

It is the investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the EC or IRB and to act accordingly.

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local requirements. In those Member States of the European Union that have implemented the European Union *Clinical Trials Directive*[52] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ECs.

Lundbeck will assess the expectedness of SAEs and inform the investigator(s) about SUSARs in the blinded SUSAR listings.

10.5 Treatment and Follow-up of Adverse Events

Patients with adverse events must be treated in accordance with usual clinical practice at the discretion of the investigator.

Non-serious adverse events must be followed up until resolution or the Completion Visit(s)/Safety Follow-up Visit, whichever comes first. At the Completion Visit(s)/Safety Follow-up Visit, information on new AEs, if any, and stop dates for previously reported adverse events must be recorded.

The investigator must follow up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial *Serious Adverse Event Form*.

SAEs that are spontaneously reported by a patient to the investigator after the Safety Follow-up Visit must be handled in the same manner as SAEs that occur during the study. These SAEs will be recorded in the Lundbeck safety database.

The investigator must follow up on patients with a clinically significant out-of-range clinical safety laboratory test value at the Completion Visit (Week 16/Visit 9) or Withdrawal Visit in accordance with usual clinical practice. If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). If further follow-up visits are made, these must be documented in the patient's medical records and not in the eCRF.

Patients who withdraw due to an elevated AST or ALT value (see section 5.4) must be followed until the values normalize or stabilize or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, prothrombin time) should be considered. A gastroenterology or hepatology consultation should also be considered.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms (eCRFs)

eCRFs will be used to collect all the data related to the study, except the external data described in section 11.1.3.

The eCRFs use third party software (Rave®) to capture data via an online system on a computer. When the investigator enters data in the eCRF (ideally during the visit or as soon as possible [<3 days] thereafter), the data will be recorded electronically in a central database

over encrypted lines, and all entries and modifications to the data will be logged in an audit trail. Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data will be reviewed and evaluated for accuracy by Lundbeck and/or representatives from CRO. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

A *Patient Binder* will be provided for each patient. The *Patient Binder* contains different types of source documents, organized by visit and type. A ballpoint pen with waterproof ink must be used to enter information in the *Patient Binder*.

11.1.2.2 Serious Adverse Event Fallback Forms

Serious Adverse Event Fallback Forms must be used when the eCRF cannot be accessed.

11.1.3 External Data

The following electronic data will be transferred by the vendor and kept in a secure designated storage area outside the eCRF:

- eDiary data
- ePRO data
- ECG results
- Clinical Safety Laboratory data
- Biobanking data: RNA, Metabolomics/Proteomics, ADA including NAb, DNA (optional)
- Biomarker analysis results
- IMP quantification results

In case of any electronic Assessments COAs/ePROs the results will be transferred by designated vendor.

11.2 Retention of Study Documents at the Site

11.2.1 eCRF Data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF until the study has been completed. After the study has been completed, all user access to the eCRF will be revoked. Renewed access to the eCRF will be given if corrections or updates to the database are required.

At the end of the study, the site will be provided with all data related to the site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the site is the responsibility of the investigator. When confirmation of receipt of the data has been received from all sites, all user access to the eCRF will be revoked. If, for some reason, the data are not readable for the full retention period (25 years or in accordance with national requirements, whichever is longer), the investigator may request that the data be re-sent.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 25 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer. Lundbeck will remind the investigator in writing of this obligation when the *Clinical Study Report Synopsis* is distributed to the site.

If off-site storage is used, a study-specific binder will remain at the site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator TMF and must be kept in a secure place by the site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator TMF Index*, a certified copy of the *Patient Identification Code List*, and a *Retrieval Form*.

When the required storage period has expired, the documents may be destroyed in accordance with regulations.

Data access

During the study, individuals responsible for monitoring the study may view personal information of study participants without a code. If this occurs, the information will be kept confidential. The patient grants permission for this access by signing the Informed Consent Form. These individuals may include the following:

- Members of the ethics committee.
- Clinical Research Organization (CRO) staff. For example, the Clinical Research Associate (CRA).
- National and international supervisory authorities. For example, the FDA, the Healthcare and Youth Inspectorate and other government regulatory agencies from other countries.

Data storage

Patient data is stored by the study site for 25 years. Coded personal data from all study participants will be archived in the secure systems held by Lundbeck for 25 years or in accordance with national requirements, whichever is longer. Please refer to section 11.2.1 of the protocol.

Standard blood samples for safety testing sent to a central laboratory (Medpace Reference Laboratories in Belgium) may be stored for a minimum of 1 year up to 3 years after analysis, as necessary and will be destroyed within 30 days after the final data transfer.

Samples for eptinezumab quantification, exploratory biomarkers and anti-drug antibody assessments will be retained at PRA Netherlands for up to 5 years after reporting of the study.

Samples for future research will stored in a biobank at Azenta, US for a maximum of 15 years.

Data Destruction

Hardcopy study-specific data will be shredded, and electronic study-specific data will be deleted when the required storage period has expired.]

12 Monitoring Procedures

Prior to allowing patients to participate in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site. The document will also list which data may be recorded directly on the eCRFs.

Only patients with eCH may be enrolled in the study. The patient's medical records are the most comprehensive source to document the patient's diagnosis. Thus, it is required that the investigator obtains copies of medical records for each patient. In case the investigator does not have medical records for a patient at his/her own clinic, the investigator must obtain copies/written summary of relevant medical records from the previous treating physician and include the pertinent documentation in the patient's medical records at the site. If original medical records are unavailable, any properly documented communication with the treating physician, letters, written summaries, photocopies of medical records, pharmacy records and specific letter templates may be used to document the eCH diagnosis and previous acute and preventive medication use for eCH, covering a period of at least 12 months prior to Screening Visit 1 and general medical history prior to the study. Information about changes in the patient's medical history, treatment for eCH and other concomitant medication that might occur between Screening Visit 1 and the Screening Visit 2 must be obtained, using the above described modalities and documented in the patient's medical records at site.

During the study, the CRA will visit the site to ensure that the protocol is being adhered to and that all issues are being recorded, to perform source data verification, and to monitor IMP accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the site's recruitment rate, and the compliance of the site to the protocol and *Good Clinical Practice*. In addition, the CRA will be available for discussions by telephone.

Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine and verify any records that are important for the evaluation of the study.

If the site is closed to the CRO monitor due to COVID-19 or other site restrictions, remote source data verification may be done, if allowed per local and site regulations. This includes the ability for Sponsors/site monitors to conduct full and thorough source document verification with access to electronic medical records (EMR).

13 Audits and Inspections

Authorized personnel from Medical, Regulatory and Clinical Quality Assurance, H. Lundbeck A/S, and quality assurance personnel from business partners may audit the study at any time to assess compliance with the protocol and the principles of *Good Clinical Practice* and all other relevant regulations.

The investigator must be aware that representatives from regulatory authorities may also wish to inspect source data, such as medical records. The investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority.

During audits and inspections, the investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may request relevant parts of medical records. No personal identification apart from the screening or randomization numbers will appear on these copies.

Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be respected at all times.

14 Protocol Compliance

Lundbeck has a “no-waiver” policy, which means that permission will not be given to deviate from the protocol.

If a deviation occurs, the investigator must inform the CRA and they must review, discuss, and document the implications of the deviation.

15 Study Termination

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study at any time. The reasons for such action may include, but are not limited to:

- safety concerns
- proven lack of efficacy of anti-CGRP agents in clinical trials sponsored by Lundbeck or competitors
- results of the planned interim analysis

[Country Specific Amendment 1 for Germany:

- safety concerns that negatively impact the benefit/risk balance of eptinezumab treatment for the study population
- proven lack of efficacy of anti-CGRP agents in clinical trials sponsored by Lundbeck or competitors
- results of the planned interim analysis
- revocation of the positive opinion or approval of the entire study
- a necessary adjustment of the maximum insured amount is not possible]

[Country Specific Amendment 1 for Netherlands:

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study in the Netherlands at any time. The reasons for such action may include, but are not limited to:

- safety concerns
- proven lack of efficacy of anti-CGRP agents in clinical trials sponsored by Lundbeck or competitors
- results of the planned interim analysis
- the approval by the Ethics Committee in charge of the Clinical Trial is irrevocably revoked;
- it can be reasonably concluded that the Clinical Trial must be terminated in the interests of the health of the Clinical Trial Subjects;
- it becomes apparent, following confirmation of the Ethics Committee that continuation of the Clinical Trial cannot serve a scientific purpose, and this is notified to the Ethics Committee;
- the Sponsor and/or the Institution (study site) become or are declared insolvent or a petition in bankruptcy has been filed against it or if one of them is dissolved;
- the principal investigator is no longer able to perform the duties of principal investigator, and no replacement can be found by mutual consent. This will result in closure of the study site.
- one of the Parties fails to comply with the obligations arising from the Agreement and, if capable of remedy, is not remedied within 30 days after receipt of written notice from the other Party specifying the non-compliance and requiring its remedy, unless failure to comply is not in reasonable proportion to the premature termination of the Clinical Trial.
- if circumstances beyond the control of the sponsor, investigator or funder make it unreasonable to require the study's continuation.

The study or part of the study will be terminated in the Netherlands if it is temporarily suspended for reasons of subjects' safety and the accredited METC gives a negative decision after assessing the reasons that led to the temporary suspension.]

If the study is terminated or suspended, the investigator must promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or Lundbeck must promptly inform the EC or IRB and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit evaluation changes after the study is terminated, the new evaluation must be provided to the EC or IRB if it will have an impact on the planned follow-up of the patients who participated in the study. If so, the actions needed to protect the patients must be described.

16 Statistical Methodology

16.1 Responsibilities

An independent CRO will perform the unblinded interim analysis. Biostatistics, H. Lundbeck A/S, will perform the statistical analyses for the clinical study report.

16.2 Analysis Sets

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

- all-patients-randomized set (APRS) - all randomized patients
- all-patients-treated set (APTS) - all patients in the APRS who received infusion with double-blind IMP
- all-patients-treated at interim set (APTS_IN) – all patients in the APRS who were among the first 204 that received infusion with double-blind IMP. Patients in the APTS that were infused on the same date, but after the first 204 will also be included.

The patients and data will be classified into the analysis sets according to these definitions at a *Classification Meeting.* For the interim analysis, the meeting will be held after the study database for the interim analysis has been released but before the unblinding for the interim analysis.

When all in patients in APRS have had the chance of completing the Placebo-controlled Period (Visit 6/Week 4), data collected in the Placebo-controlled Period will be cleaned and locked. A *Classification Meeting* will be held after the database release for the reporting of the Placebo-controlled Period but before the blind has been broken. Patients included in the interim cut-off will not be re-classified. Analyses specified in the SAP for data collected in the Placebo-controlled Period will then be performed. After all patients have completed the study, data will be cleaned and locked, the database will be released and the remaining analysis in the SAP will be performed.

Investigators and patients will be informed about which treatment (eptinezumab 400 mg or placebo) the patients received in the Placebo-controlled Period only after the last patient has completed the study. Efficacy analyses for the interim analysis will be based on APTS_IN, and the final efficacy analyses of the Placebo-controlled Period will be based on APRS.

Demographics, Baseline characteristics, and safety tables (including exposure and medications) will be based on APTS.

16.3 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, 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.

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

Resolution of the cluster headache bout is defined as the day after the last day of the cluster headache bout.

16.4 Patient Disposition

Patient disposition will be summarized by treatments and include the number of patients in each analysis set who completed or withdrew from treatment, as well as the number of patients in each analysis set (APRS, APTS, APTS_IN, and).

The number of patients who withdrew will be summarized by period and treatments and primary reason for withdrawal as well as by period and treatments and all reasons for withdrawal.

16.5 Demographics and Baseline Characteristics

Demographics (sex, age, and race), baseline characteristics (height, weight, and BMI), baseline efficacy variables, and other disease characteristics will be summarized by period and treatments.

16.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarized by anatomical therapeutic chemical (ATC) code and generic drug name by period and treatments.

16.7 Exposure

All patients in the APTS are expected to receive at least one infusion of the IMP. The number of patients infused and patients who had their infusion interrupted will be summarised by visit and treatment. Patients whose infusion took more than 45 mins and patients who had their infusion interrupted will be listed with period and treatment, infusion start date/time and end date/time, infusion related reactions, and reasons if any.

16.8 Efficacy Analyses

16.8.1 General Efficacy Analysis Methodology

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

All tables and graphs will be presented by treatment.

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

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

16.8.1.1 Primary Estimand

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

Intercurrent Events

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

- Abortive medication for cluster headache (Triptans or Oxygen)
- Preventive medication for cluster headache (Classified by investigator clinician among the concomitant medication)
- Transitional treatment for cluster headache (GON block and oral steroids)
- Interruption of IMP: Infusion stopped prematurely

Attributes of the primary estimand

The primary estimand has the following attributes:

- The **treatment condition of interest** will be the comparison of eptinezumab 400 mg to placebo without the use of transitional treatment, and with or without the use of abortive or preventive medication for cluster headache
- The **population of interest** will be all patients with episodic cluster headache that fulfil the inclusion and exclusion criteria

- The **endpoint to be obtained to address the clinical question** is change from Baseline in the number of weekly attacks (Weeks 1-2)
- The **other intercurrent events:** use of transitional treatment or interruption or prematurely stopping IMP infusion will be addressed by treatment policy strategies
- The **population level summary** will be the mean difference in the primary endpoint between eptinezumab 400 mg and placebo.

16.8.2 Strategies for Addressing Intercurrent Events in Primary Estimand

Clinically relevant strategies to manage the intercurrent events are selected based on the following hypothesis for likely outcomes given the intercurrent events.

It is hypothesised, that for an individual patient, daily attacks may increase a little early in the bout, i.e. during Screening Period 2 and potentially during Week 1, but after which the daily attacks reach a "plateau" for a period of time and start decreasing in frequency and intensity indicating that the bout is coming to an end. The minimum expected duration of CH bout in this study is 6 weeks. Thus, if effective the active treatment should result in a decrease in the symptoms level, and more so than placebo regardless of whether the patients continue to report data in the eDiary for the study, since the infused drug continues to be available in the body well beyond the first 2 weeks.

Therefore, if penalization is required it is not possible to use baseline observation carried forward, since baseline values could be better than Week 1 values. For this reason, penalization will be done using the imputation according to the placebo treatment.

Use of abortive rescue medication

Abortive medication for an individual attack is typically taken after the start of the attack and may reduce the severity and duration of the attack, for which it was used, but is not expected to have a preventive effect on future attacks even if on the same day.

Use of abortive medication for attacks will be addressed with a treatment policy strategy, using the reported number of attacks regardless of any abortive medication used.

Use of preventive medication

Preventive medications usually require up-titration (approximately 2 weeks) before the effect is established, hence these are not expected to affect the symptom level during the first 2 weeks of the Placebo-Controlled period.

Use of preventive medication will be addressed with a treatment policy strategy, using the reported observations regardless of any preventive medication initiated.

Use of transitional treatment for eCH

Transitional treatments, such as GON block and oral steroids, are expected to impact the number of future attacks with an almost immediate effect.

Use of transitional treatment for cluster headaches will be addressed using a hypothetical strategy, assessing effect as if no transitional treatment would be available. Under these hypothetical circumstances it is assumed that the effect would be similar to other patients with similar previous scores on the same randomised treatment.

Interruption of infusion with IMP

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

16.8.3 Primary Analysis of the Primary Endpoint

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

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

The strategy for imputation of missing data is given below and in details in the SAP:

Weekly scores are calculated using pro-rating, when data has been observed for at least 4 out of 7 days, with the weekly score = the average daily score x 7.

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

The pMI will generate 200 simulated data sets with complete assessment of number of weekly attacks for Weeks 1, 2, 3, and 4. Each of these 200 data sets will be analysed using the following MMRM model:

The MMRM model based on data from all 4 weeks in the PBO-controlled period will include the following fixed effects: week (1, 2, 3, 4), country, and treatment as factors, baseline score as a continuous covariate, treatment-by-week interaction, and baseline score-by-week interaction. An unstructured variance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

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

The 200 results will be weighted together using Rubin's rule to obtain a pMI estimate, confidence interval, and p-value.

16.8.4 Details are provided in the SAP.Sensitivity Analyses of the Primary Endpoint

The impact of missing data in the derivation of the number of weekly attacks averaged across Weeks 1-2 and the impact of the use of transitional treatment will be evaluated by applying different methods of imputation. Details will be described in the SAP.

16.8.5 Analysis of the Key Secondary Endpoints

Key secondary endpoints based on eDiary will be imputed along the lines used for the primary endpoint. Details will be provided in the SAP.

The continuous key secondary endpoints (Change from Baseline in the number of weekly times an abortive medication was used (Weeks 1-2), and Change from Baseline in the number of weekly days with <3 attacks per day (Weeks 1-2)) will be analysed using the MMRM model presented in the section on primary analysis using the baseline value of the variable as baseline.

The Change from Baseline in the number of daily attacks (Days1-3) will be analysed using an analysis of covariance (ANCOVA) including treatment and country as factors and baseline number of weekly attacks as covariate.

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

When using the terminology Weeks 1-2 or Days 1-3 for example, the average across the first two weeks or the first three days is measured.

Response used as a key secondary endpoint will be analysed using logistic regression where region and treatment are included as fixed factors and baseline number of weekly attacks is included as covariate.

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

16.8.6 Testing Strategy

Primary endpoint

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

Key secondary endpoints

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

A two-sided significance level of 0.05 will be used for the formal testing strategy.

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

Step 1

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

Step 2

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

Step 3

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

16.8.7 Analysis of the Secondary Endpoints

The continuous secondary endpoints (with the exception of PGIC) will be analysed using a MMRM model similar to the one described in the primary endpoint section.

The PGIC score will be analysed using an MMRM with number of attacks in the Screening Period 2 as covariate instead of baseline score.

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

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

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

16.8.8 Analysis of the Exploratory Endpoints

The continuous exploratory endpoints will be analysed using a MMRM model similar to the one described in the primary endpoint section.

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

A Kaplan-Meier plot of time from first infusion of eptinezumab to resolution of cluster bout within 16 weeks will be provided for the 400mg eptinezumab treatment.

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

The following endpoints will be presented using descriptive statistical analyses:

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

16.8.9 Analysis of Subgroups

Details of subgroup analyses will be specified in the SAP.

16.9 Safety Analyses

16.9.1 Analysis 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 during or after administration of the first dose of IMP, or a pre-treatment adverse event that increases in intensity or becomes serious during or after administration of the first dose of IMP

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarized by period and treatment.

Allocation of TEAEs to Study Periods

TEAEs will be allocated to study periods (these will be defined in the Statistical Analysis Plan).

16.9.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, vital signs, weight, and ECG parameter values will be summarized by period and treatment. Potentially clinically significant (PCS) values will be flagged and summarized.

The number of patients with ADA will be summarised by period and treatment. The number of patients with NAbs will be summarised by period and treatment.

Non-suicidal self-injury behaviour (considered separately) and no suicidal ideation or behaviour or the worst suicidal ideation or behaviour will be summarised by period and treatment.

16.10 Interim Analyses

When 204 patients have been randomised, have received IMP and have had the chance of completing the Visit 6 (Week 4), the data will be cleaned and an interim analysis will be performed for the APTS_IN. If the estimated treatment effect is less than 1/3 of the expected effect size (3.00/3 = 1). Lundbeck may decide to stop the study for futility.

The interim analysis will be performed by an independent CRO, and the evaluation methods used in the interim analysis is the same as for the primary endpoint.

The SAP will be finalized prior to the interim analyses.

The independent CRO will inform a predefined group of Lundbeck employees whether the criterion for the interim futility have been met or not. No further details of the interim analysis results will be provided.

Details of the interim process will be described in a separate *Interim Analysis Charter*.

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

Further details will be described in an *Interim Statistical Analysis Plan* that will be prepared by Biostatistics, H. Lundbeck A/S, before the study is partially unblinded.

16.11 Sample Size and Power

Goadsby (2019)[35] describes a study in eCH, where the first 4 weeks have a design similar to this study. The difference between galcanezumab and placebo in change from baseline in weekly frequency of attacks at Week 1 is estimated at -1.5 attacks, and at Week 2 is estimated at -4.4 attacks. The average difference to placebo across Week 1 and Week 2 is estimated at 3.0. Based on the CI presented in the publication, the SD at Week 1 is estimated at 9.2 and the SD at Week 2 is estimated at 11.1. Assuming that the correlation between Week 1 and Week 2 is 0.56, the SD for the average of Week 1 and 2 will be SD = 9.0.

Assuming a difference of eptinezumab to placebo of -3.0 attacks with an SD = 9.0, 144 patients per treatment will provide 80% power for seeing an effect using a two-sided 5.0% significance level. Since the estimated treatment difference may be slightly decreased due to the use of pMI, an additional 5% of patients have been added. This yields a total of 152 patient per treatment.

16.12 Statistical Analysis Plan

A *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by Biostatistics, H. Lundbeck A/S, before the study is unblinded.

17 Clinical Study Report and Publications

17.1 Data Ownership

The data collected in this study are the property of Lundbeck.

17.2 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by Regulatory Medical Writing, H. Lundbeck A/S.

17.3 Summary of Clinical Study Results

Upon completion of the study and when the study results are available, the patient has the right to be informed by the investigator about the overall study results.

17.4 Publications

The results of this study will be submitted for publication, in accordance with the Lundbeck policy and regardless of the study outcome.

Lundbeck will submit results information:

- to ClinicalTrials.gov
- to EudraCT

The primary publication based on this study must be published before any secondary publications. Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[53]

18 Indemnity and Insurance

In the event of study-related injuries or deaths, insurance for the patients and indemnity of the investigators and those of their employees, servants, or agents whose participation in this study has been documented are provided. Insurance and liability will be in accordance with applicable laws and *Good Clinical Practice*.

19 Finance

19.1 Site Agreements

The financial agreements with each site are addressed in one or more documents. Both parties must sign the agreements before each site is initiated.

19.2 Financial Disclosure

All the investigators, including sub-investigators, and raters participating in the study must complete a Financial Disclosure Form.

19.3 Equipment

Equipment owned or rented by Lundbeck that has been provided to the sites for use during the study must be returned at the end of the study.

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Appendix I
Clinical Study Protocol
Authentication and Authorization

Clinical Study Protocol
Authentication and Authorization

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

Study No.: 19386A

Edition No.: 5.0

Date of edition: 03 April 2023

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

Authentication

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

International study manager: PPD

Clinical research scientist: PPD

Head of Biostatistics: PPD

Head of Global Medical Safety: PPD

Authorization

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Therapeutic Area Lead: Bjørn Sperling

Appendix II
Recent and Concomitant Medication
Disallowed or Allowed with Restrictions

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

In the table below, recent and concomitant medications that are disallowed or allowed with restrictions with respect to their use prior to or during the study are listed.

Drug Class	Details
Any investigational drug	• Do not use within 30 days or 5 plasma half-lives (whichever is longer) prior to the Screening Visit 2.
Anticonvulsants	Allowed with restrictions: • For preventive treatment for CH, see *Cluster Headache Therapies* • For indications other than cluster headache: – Allowed if prescribed for indications other than epilepsy.
Cluster Headache Therapies	• **Abortive treatment** The following abortive therapy for cluster headache attack is allowed: – high-flow oxygen; – oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; – acetaminophen, NSAIDs, – dihydroergotamine (up to 3 days per week) or ergot derivatives (except methergine) – Octreotide – Opioids are allowed with restrictions, maximum 2 days per week • **Transitional treatment** Disallowed for 30 days prior to the Screening Period 2 and until the end of Week 4: – Greater occipital nerve (GON) block – Injected and oral corticosteroids • **Preventive treatment:** Stable dose for one month prior to Screening visit 2 and until the end of Week 4: – Verapamil maximum dose 240 mg/day – Topiramate maximum dose 50 mg/day – Gabapentin maximum dose 1200 mg/day – Valproate maximum dose 900 mg/day – Candesartan maximum dose 16 mg/day – Lithium maximum dose 12 mmol/day and/or se-lithium less than 0.6 mmol/l Allowed at any time with a restriction on the dose: – Melatonin maximum dose 9 mg/day Other medicines used as preventive treatment for CH are disallowed for one month prior to Screening visit 2 and until the Safety Follow-Up Visit

Drug Class	Details
	• **Other treatment and interventions:** Disallowed for 4 months prior to the Screening Period 2 and until the Safety Follow-Up Visit: – Botulinum toxin type A or B, that was administered in the head or neck area for treatment of cluster headache or other disorders, or for cosmetic use. Disallowed for 30 days prior to the Screening Period 2 and until the Safety Follow-Up Visit: – indomethacin – any other cranial or extracranial nerve block – any neuromodulation treatment – Gamma knife or other invasive procedures
Anti CGRP therapies	• Anti-CGRP therapies are disallowed for ≤5 half-lives for mAbs and ≤1 month for gepants prior to Screening Visit 2
Antihypertensives	• Candesartan and Verapamil allowed with restrictions- see *Cluster Headache Therapies* • Other medications in the same class are allowed
Anti-impotence agents	• Allowed if the dose has been stable for at least 12 weeks prior to the Screening Period 2 and remains stable until the Completion Visit (Week 16)
Cannabinoids	• Restrictive use (as per investigator judgement) of cannabinoids is allowed*
COVID-19 vaccine	• If possible, COVID -19 vaccine should not be administered within 1 week prior to Screening Visit 2 and until the Primary Outcome Visit (Week 2). • If possible, COVID-19 vaccine should not be administered within ±3 days of the second IMP infusion at Week 4.
Ergot alkaloids	• Methergine is disallowed for 14 days prior to the Screening Period 2 and until the Safety Follow-Up Visit • Dihydroergotamine allowed as abortive treatment for up to 3 days per week • Other medications in the same class are allowed
Steroids: Oral and Systemic	Allowed with restrictions: • For transitional treatment for CH, see *Cluster Headache Therapies* • For indications other than cluster headache: - Disallowed for 30 days prior to Screening Visit 2 and until end of Week 4 - Short-term treatment (maximum 3 days, followed by potential tapering) is allowed from end of Week 4 until the SFU Visit
Illicit substances	• Disallowed for 2 months prior to the Screening Period 1 until the Safety Follow-Up Visit: Psilocybin (mushrooms), LSD, or 2-bromo-LSD, or other illegal drugs. Restrictive use of cannabinoids is allowed, please see “Cannabinoids”

* The eligibility of patients who occasionally use cannabinoids (confirmed by either anamnesis or finding at Urine drug screen at Screening Visit 2) must be based on a confirmation from the investigator that the patient does not meet Exclusion criteria 10, 24 and 25.