Clinical Study Protocol

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

Eptinezumab

Study No.:	19385A (CHRONICLE)
EudraCT/IND No.:	2020-001968-28 / 151358
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Synopsis – Study 19385A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Eptinezumab
Study Title Interventional, open-label, fixed-dose multiple administration study to evaluate long-term treatment with eptinezumab in patients with chronic cluster headache	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • To evaluate the long-term safety and tolerability of eptinezumab in patients with chronic cluster headache (cCH)	• Endpoints for the primary objective: – adverse events – absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values – potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values – development of specific anti-eptinezumab antibodies (ADA) including neutralizing antibodies (NAbs) – Columbia-Suicide Severity Rating Scale (C-SSRS) score

Secondary Objectives • To evaluate the efficacy of eptinezumab in patients with cCH	• Endpoints for the secondary objective (efficacy): – Conversion from cCH to episodic cluster headache (Week 0 to Week 48): Number of patients with no cluster headache attacks for ≥3 consecutive months (≥13 consecutive weeks) – Change from baseline in weekly number of times an abortive therapy (oxygen and/or triptans) was used (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Change from baseline in the average number of weekly attacks (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Change from baseline in the 5-point self-rating pain severity scale (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Response: ≥30% reduction in number of weekly attacks (calculated for each infusion with eptinezumab, based on the average across the first 4 weeks after the infusion) – Response: ≥50% reduction in number of weekly attacks (calculated for each infusion with eptinezumab, based on the average across the first 4 weeks after the infusion) – cCH remission (Week 0 to Week 48): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks) – cCH remission (Week 0 to Week 12): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the first and second infusion) – cCH remission (Week 12 to Week 24): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the second and third infusion) – cCH remission (Week 24 to Week 36): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the third and fourth infusion) – cCH remission (Week 36 to Week 48): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks within the first 12 weeks after the fourth infusion) – Number of patients who received a transitional therapy during the Treatment Period (Week 0 to Week 48) – Patient Global Impression of Change (PGIC) score (assessed monthly after the first eptinezumab infusion) – Change from baseline in Sleep Impact Scale (SIS) domain scores (at each infusion and 4 weeks after each infusion)

Secondary Objectives (continued) • To evaluate the efficacy of eptinezumab in patients with cCH (continued)	• Exploratory endpoints for the secondary objective (efficacy): – Change from baseline in the average number of monthly attacks (per 4-week intervals after each eptinezumab infusion) – Change from baseline in the 5-point self-rating pain severity scale (taking the average across 4-week intervals after each eptinezumab infusion) – Response: ≥30% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Response: ≥50% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Response: 100% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Change from baseline in monthly number of times an abortive therapy (oxygen and/or triptans) was used (per 4-week interval after each eptinezumab infusion)
• To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity	• Endpoints for the secondary objective: – Change from baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L) at Weeks 4, 16, 28, 40 and 48 – Health Care Resources Utilization (HCRU) at baseline, Weeks 4, 16, 28, 40 and 48 – Change from baseline in the Work Productivity Activity Impairment: General Health second version (WPAI:GH2.0) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Weeks 4, 16, 28, 40 and 48
Exploratory Objective • To explore the target engagement of eptinezumab to calcitonin gene-related peptide (CGRP)	• Endpoint for the exploratory objective: – Change from baseline to each study time point in CGRP: CGRP-eptinezumab complex, free CGRP

Study Methodology

- This is an interventional, open-label, fixed-dose multiple administration study to evaluate the long-term treatment with eptinezumab in patients with cCH.
- The target population for this study is defined as patients with cCH, based on the *International Headache Society* International Classification of Headache Disorders third edition (IHS ICHD-3) classification, with documented evidence of cCH prior to screening and confirmed via prospectively-collected information in the eDiary during the Screening Period.
- The total study duration from the Screening Visit to the Safety Follow-up (SFU) Visit is approximately 60 weeks and includes Screening Period (4 weeks), Treatment Period (48 weeks), and SFU Period (8 weeks).
- Eligible patients will receive four infusions with eptinezumab 400 mg at 12-week intervals at Day 0 (Visit 2), at the end of Weeks 12 (Visit 5), 24 (Visit 8) and 36 (Visit 11), administered as an intravenous (IV) infusion over 45 minutes (+15 minutes).
- The SFU Visit will take place at Week 56 (Visit 15) that is 20 weeks (5 half-lives) after the last eptinezumab administration.
- 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 eptinezumab 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 eptinezumab 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 last eptinezumab administration.
- Eligibility will be assessed during the Screening Period and before the first administration of eptinezumab at the Baseline Visit (Day 0/Visit 2).
- Study visits:
  - The following visits will be site visits: Screening Visit at Week -4 (Visit 1), Investigational Medicinal Product (IMP) Visits at Weeks 0, 12, 24 and 36 (Visits 2, 5, 8 and 11), Completion Visit at Week 48 (Visit 14) and SFU Visit at Week 56 (Visit 15) or Withdrawal Visit, if applicable.
  - All other study visits will be phone contact visits.
  - In exceptional situations to be approved by the Contract Research Organisation's (CRO) medical monitor, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and eptinezumab administration, while the remaining assessments (eDiary, electronic patient-reported outcomes [ePROs], C-SSRS, and investigator evaluations) can be conducted remotely as virtual clinic visits in line with the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) guidance.
- Patients will be assigned an eDiary at the beginning of the Screening Period (Visit 1, Week -4) and will be required to complete it:
  - Daily - during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40).
  - Weekly - for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48.
- During the study visits with eptinezumab infusion, eDiary and ePROs must be completed prior to infusion and prior to any interaction with the clinical site staff.
- At these visits, safety assessments will be performed before and after the infusion. Safety assessments before eptinezumab infusion consists of vital signs including body temperature, weight, concomitant medications, adverse events, ECG, blood sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, and ADA including NAb), urine sampling (for clinical safety laboratory and pregnancy tests) and C-SSRS. Safety assessments after eptinezumab infusion consists of vital signs including body temperature, and adverse events.

• Blood samples for exploratory eptinezumab quantification, and ADA and NAbs assessments will be collected at Visits 2, 5, 8, 11, 14 (or at Withdrawal Visit for patients, who withdraw from the study) and at SFU Visit (Visit 15). • The study design is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarised in Panel 2.
Number of Patients Planned 125 patients recruited from specialist settings are planned to be enrolled and receive treatment with eptinezumab, allowing for 100 patients to complete.

Target Patient Population

Main Inclusion Criteria

- The patient has a diagnosis of cCH as defined by IHS ICHD-3 classification with a history of cCH of at least 12 months prior to the Screening Visit.
- The patient has a medical history of onset of cluster headache at ≤50 years of age.
- The patient has an adequately documented record of previous abortive, transitional and preventive medication use for cCH, for at least 12 months prior to the Screening Visit.
- The patient has during the Screening Period, based on prospectively-collected information in the eDiary, a cluster headache attack frequency of (*this requirement should not be shared with the patient*):
    a. minimum of 14 cluster headache attacks for the 28-day Screening Period
- The patient is able to distinguish cluster headache attacks from other headaches (such as tension-type headaches, migraine).
- The patient has demonstrated compliance with the eDiary by entry of data for at least 24 out of 28 days during the 4-week Screening Period.
- The patient is aged ≥18 and ≤75 years at the Screening Visit.

Main Exclusion Criteria

- The patient has experienced failure on a previous treatment targeting the CGRP pathway (anti-CGRP monoclonal antibodies [mAbs] and gepants).
- The patient has a history of severe drug allergy or hypersensitivity or known hypersensitivity or intolerance to the IMP or its excipients.
- The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, complex regional pain syndrome).
- The patient has a history or diagnosis of chronic paroxysmal hemicrania.
- The patient has a history or diagnosis of chronic tension-type headache, 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 neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or longer than 1 hour).
- Patients with a history of epilepsy.
- Patients with a lifetime history of psychosis, bipolar mania, or dementia. 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 the Screening Visit.
- The patient is, at the Screening Visit or at the Baseline Visit, 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, vascular ischaemia or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
- The patient has been previously tested positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or Hepatitis C virus antibody (anti-HCV).

– *The following recent and concomitant medications are disallowed or allowed with restrictions 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 the Screening Visit.
b. Botulinum toxin type A or B, administered in the head or neck area for treatment of cluster headache or other disorders, or for cosmetic use, is disallowed for 4 months prior to the Screening Visit and until the SFU Visit.
c. Psilocybin (mushrooms), lysergic acid diethylamide (LSD), or 2-bromo-LSD, or other illegal drugs are disallowed for two months prior to the Screening Visit and until the SFU Visit.
d. Greater occipital nerve (GON) block, injected and oral steroids (used for headache treatment) are disallowed for 30 days prior to the Screening Visit and during the Screening Period.
e. Injected and oral steroids for indications other than CH:
    i. Disallowed during the Screening Period
    ii. Short-term treatment (maximum 3 days, followed by potential tapering) is allowed from Baseline until the SFU Visit
f. The following therapies are disallowed for 30 days prior to the Screening Visit and until the SFU Visit:
    i. any other cranial or extracranial nerve block;
    ii. any neuromodulation treatment;
    iii. gamma knife or other invasive procedures.
g. Methergine is disallowed for 14 days prior to the Screening Visit and until the SFU Visit.
h. The following recent and concomitant medications are allowed with restrictions prior to or during the study (the list is not comprehensive): Stable dose (with restrictions on the maximum dose for lithium only) for 1 month prior to the Screening Visit and during the Screening Period: verapamil, topiramate, gabapentin, valproate, candesartan, lithium and indomethacin. Initiation, discontinuation and change of dose are allowed during the Treatment Period and the SFU Period, if clinically indicated.
i. Melatonin is allowed at any time. Initiation, discontinuation and dose modification are allowed during the Treatment Period and the SFU Period.
j. Dihydroergotamine is disallowed for use as a preventive treatment.
k. Abortive therapies for cluster headache attack are allowed at any time during the study: high-flow oxygen; oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (allowed for not more than 3 times per week) or ergot derivatives, octreotide.
l. Opioids and cannabinoids are allowed with restrictions.

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.

Eptinezumab will be administered at Day 0 and at Weeks 12, 24 and 36, by IV infusion over 45 minutes (+15 minutes).

Assessment Details

The assessments are summarised 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 cluster headache eDiary daily during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40) and weekly for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48. The eDiary consists of applications and reports which will be used to derive the cluster headache endpoints and abortive medication use. The eDiary will be distributed to each patient at the Screening Visit after patient training on eDiary use by the clinical site staff. The eDiary data from the 4-week Screening Period will be used to determine eligibility criteria, baseline cluster headache characteristics and eDiary compliance. Ongoing evaluation of eDiary compliance will be performed by the clinical 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/all of the time/very satisfied) to 5 (never/none of the time/very dissatisfied). Scores by domains are ranging from 0 to 100; items within each domain are summed and transformed using a formula. A higher score indicates better quality of life.

Health Care Resource Utilization (HCRU)

Cluster headache-specific HCRU 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 study.

Statistical Methodology

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

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

The safety and tolerability analyses, and the exposure, disposition, and demographics and baseline characteristics will be based on the APTS. The efficacy analyses will be based on the FAS.

Primary analysis

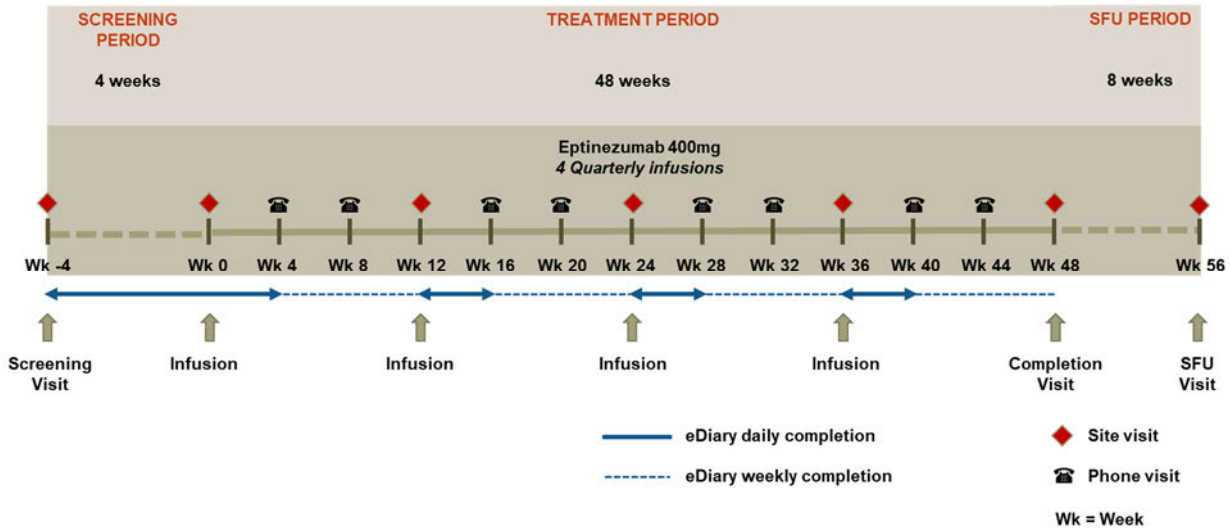
- The primary objective of the study is to evaluate the long-term safety and tolerability of eptinezumab in patients with cCH. This will be evaluated based on the collected data on adverse events, vital signs, weight, ECGs, clinical safety laboratory test values, C-SSRS, ADA and NAbs. Adverse events will be summarised for the full study and by 3-month periods, absolute values and changes from baseline for vital signs, weight, ECGs, clinical safety laboratory test values will be summarised by visit. The number of patients exceeding the PCS values will be tabulated. The incidence, kinetics and magnitude of ADA and NAb response(s) will be evaluated.

Secondary analysis

- Details on derivations and imputations of eDiary data (daily or weekly data entries), as well as sub-group analyses, will be described in the Statistical Analysis Plan (SAP).
- For continuous endpoints, descriptive statistics for absolute values and changes from baseline, when appropriate, will be provided by visit. In addition, continuous endpoints will be modelled using mixed models for repeated measurements (MMRM) including baseline score, visit and baseline interacting with visit, if applicable. The estimated means, standard errors and confidence intervals (CIs) will be provided by visit. For response variables the counts, percentages and CI will be presented by visit.

Testing Strategy No formal testing will be done.
Sample Size Considerations In line with the International Council for Harmonisation (ICH) E1 guideline,[1] this study aims at providing data in 100 patients exposed to eptinezumab for 1 year. Dodick (2020),[2] in patients suffering from cCH included in a 12-week study, reports less than 4% withdrawals. In the European Union Drug Regulating Authorities Clinical Trials (EudraCT) report for study NCT02964338,[3] in patients suffering from cCH, approximately 7% of patients dropped out from the first 12-week period; the withdrawals due to the "sponsor terminated study" are not included as a reason for withdrawal. As the withdrawal rate for a long-term study like the current study is unknown, 125 patients are planned to be enrolled and treated, allowing for 100 patients to complete, with a withdrawal rate of 20%. The withdrawal rate will be monitored during the study conduct, and if a clear deviation from the assumed withdrawal rate is observed, the number of patients enrolled and treated might be increased to ensure that data is available for a sufficient number of patients with long-term exposure.

Panel 1 Study Design



The study consists of Screening Period (4 weeks), Treatment Period (48 weeks), and SFU Period (8 weeks). Eligible patients will receive four IV infusions with eptinezumab 400 mg administered at 12-week intervals. For all patients who complete the study, a SFU Visit will be conducted 20 weeks (5 half-lives) after the last infusion of eptinezumab, that is at Week 56 (Visit 15). For patients who withdraw from the study, the SFU Visit will be conducted 20 weeks (5 half-lives) after their last eptinezumab infusion.

Panel 2 Study Procedures and Assessments

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

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

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

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

a This visit should be a site visit.

b For phone visits, the 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 adverse events and concomitant medications.

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

d 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.

e If the date of a clinic visit or phone contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit (Day 0/Visit 2).

f At the Screening Visit, the patient will be asked to sign the main Informed Consent Form (ICF), and the ICF for blood sampling for pharmacogenetics (optional). Depending of the country requirements, the number of

ICFs may be different. Under exceptional circumstances, the discussion with the 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. 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.

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

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

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

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

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

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

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

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

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

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

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

r Biobank may be excluded or optional per local regulation.

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

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

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

v 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.

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

x For women of childbearing potential, pregnancy test at the Screening Visit and the SFU Visit is to be

conducted using serum beta-human chorionic gonadotropin (β-hCG). At all other visits, urine pregnancy testing will be performed and in case of a positive finding, further confirmatory testing will be performed via serum β-hCG.

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

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

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Appendices

List of Panels

List of Abbreviations and Definitions of Terms

β-hCG	beta-human chorionic gonadotropin
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
APES	all-patients-enrolled set
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
cCH	chronic cluster headache
CGRP	calcitonin gene-related peptide
CI	confidence interval
C_{max}	maximum observed concentration
COA	clinical outcome assessments
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	Contract Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTFG	Clinical Trials Facilitation and Coordination Group
DNA	deoxyribonucleic acid
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
GON	greater occipital nerve
HBsAg	hepatitis B surface antigen
HCRU	Health Care Resources Utilization
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3	International Classification of Headache Disorders third edition
ICMJE	International Committee of Medical Journal Editors
IHS	International Headache Society
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRT	interactive response technology
ISR	incurred sample re-analysis
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
LSD	lysergic acid diethylamide
mAb	monoclonal antibody
MMRM	mixed model for repeated measurements
NAb	neutralizing antibody
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
PCR	polymerase chain reaction
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
QP	qualified person
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SFU	safety follow-up
SIS	Sleep Impact Scale
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal-elimination-half-life
TEAE	treatment-emergent adverse event
TMF	trial master file
US FDA	United States Food and Drug Administration
VAS	visual analog scale
V_c	volume of distribution
WPAI:GH2.0	Work Productivity and Activity Impairment: General Health second version

Major Changes Since Last Edition

The following summarizes the major changes since the last edition of this CSP.

Chapter/ Section Number	Chapter/Section Title	Change
Synopsis	Main Inclusion Criteria	*Updated*: Inclusion criterion changed from: "The patient has had a diagnosis of cluster headache at <50 years of age" to "The patient has a medical history of onset of cluster headache ≤50 years of age".
Synopsis	The following recent and concomitant medications are disallowed or allowed with restrictions prior to or during the study (the list is not comprehensive)	Steroids (oral and injectable) allowed with restrictions for indications other than CH.
3.2	Rationale for the Study Design	*Added:* Clarification that fulfilment of criteria for cCH, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the screening period and the investigator responsibility to review and decide on the eligibility of the patient based on data in the eDiary.
5.3	Selection Criteria	*Updated*: Inclusion criterion #7 changed from: "The patient has had a diagnosis of cluster headache at <50 years of age" to "The patient has a medical history of onset of cluster headache at ≤50 years of age".
8.2.4	Extension of Screening Period	*Added*: Allowance for extension of the screening period if the patient does not fulfil Exclusion criterion N°18 and criteria can be met by allowing additional 7 days in the Screening period.
8.9	Unscheduled Visits	*Added:* Description of unscheduled visits.
9.1.2	Diagnostic Assessments	*Added*: Definition of an eDiary compliant day has been specified.
Appendix II	Recent and Concomitant Medication: Disallowed or Allowed with Restrictions	*Updated:* Clarified that cannabinoids are allowed if prescribed or if locally approved. Clarified that the maximum dose of lithium must be as per the country-specific guidelines for management of patients with CH AND the se-lithium level must be below the toxic level based on the reference ranges of the local laboratory. Steroids (oral and injectable) allowed with restrictions for indications other than CH.

1 Introduction

1.1 Background

1.1.1 Overview

Chronic cluster headache (cCH) is a rare but disabling primary headache disorder characterized by attacks of intense unilateral headache, frequently associated with autonomic symptoms such as lacrimation, conjunctival injection, and nasal congestion (*International Headache Society* International Classification of Headache Disorders third edition [IHS ICHD-3]).[4] The diagnosis of cCH is distinctly recognized and defined by the ICHD-3. The natural course of illness of cCH can be conceptualized as cluster headache attacks occurring for 1 year or longer without remission, or with remission periods lasting less than 3 months.

The social impact of cluster headache is considerable[5] and is associated with considerable direct and indirect economic consequences.[6] Cluster headache has a prevalence of 0.1% with a 2 to 6 times higher average incidence rate for males compared to females.[7] However, the ratio might be lower due to misdiagnosis of cluster headache in females compared to males.[8] The lifetime prevalence of cluster headache, based on a meta-analysis, showed a mean prevalence of 124 per 100,000, where episodic form was 6 times more prevalent than the chronic form.[7]

There are significant unmet needs for just about every clinical aspect of cluster headache, particularly related to the severity of the disease, the diagnostic challenges and the available treatment options. Most patients experiencing cluster headache attacks rate their pain intensity as near to or at the worst pain imaginable (using a 10-cm Visual Analog Scale [VAS]).[9]

The pharmacological armamentarium in cluster headache consists of acute / abortive therapies, transitional therapies and preventive treatments. First line of acute treatment is sumatriptan administered subcutaneously[10, 11, 12] and inhalation of 100% oxygen.[13, 14, 15, 16] Transitional therapies are often used to relieve the patient until the preventive agents are adequately titrated, and consists of oral steroids or greater occipital nerve (GON) blocks.[17, 18] The currently available preventive pharmacological treatments are unspecific, insufficient, and hampered by side-effects. Preventive treatment aims to reduce attack frequency with verapamil being first-choice, but only 50 to 80% of cluster headache patients are responders;[19] 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[20, 21] and high cost.[22] In the clinic, several types of treatment are combined in the effort to provide relief to the patients and improve 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.[23] Cluster headache patients have higher CGRP levels compared to migraine patients and healthy controls.[24] As in migraine,[25] CGRP levels are altered during attacks. Recently, a provocation study supported the central role of CGRP involvement in cluster headache as infusion of CGRP induced attacks in patients with cCH and in patients with episodic cluster headache in an active bout.[26]

Eptinezumab is a humanised monoclonal antibody (mAb) that inhibits the action of CGRP and is approved by the United States Food and Drug Administration (US FDA) as the first and only intravenous (IV) preventive treatment for migraine. Results from two placebo-controlled, Phase III studies showed that eptinezumab led to a significant reduction in the number of monthly migraine days in patients with migraine: both in episodic and chronic migraine (study ALD403-CLIN-006,[27] and ALD403-CLIN-011,[28] respectively). The IV administration of eptinezumab and its fast onset of action make it a good candidate for treatment of patients with cluster headache because an early effect is needed due to the relatively short duration and intense severity of the attacks. Cluster headache and migraine share some similarities, including the active role of CGRP in the disease biology, and put together with the clinical efficacy in migraine, the evidence supports the hypothesis of eptinezumab being effective in the treatment of cluster headache.

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*[29] 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 no-observed-adverse-effect level (NOAEL) of 150 mg/kg/dose supports a 103-fold or 123-fold safety margin by maximum observed concentration (C_{max}) or area under the curve (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.[29]

In conformance with applicable guidance documents, a complete package of reproductive/development toxicity studies were conducted. In these studies, administration of eptinezumab by IV 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.

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 oedema, 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;[30] 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 in migraine patients is composed of five completed studies to date; including two pivotal placebo-controlled studies (Phase III study in frequent episodic migraine [ALD403-CLIN-006],[27] and Phase III study in chronic migraine [ALD403-CLIN-011]).[28] A Phase III study (18903A)[31] has been conducted to assess treatment of eptinezumab in patients experiencing an acute attack of migraine.

A further global Phase III placebo-controlled study is initiated to evaluate the efficacy and safety of eptinezumab in patients with episodic cluster headache (19386A). This study is designed to demonstrate a statistically significant effect of eptinezumab on number of attacks during the cluster headache bout.

Eptinezumab is administered by 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 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.

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.[32] Nevertheless, the co-administration of eptinezumab in combination with sumatriptan was investigated in Study ALD403-CLIN001.[29] The co-administration of sumatriptan did not appear to alter the single dose pharmacokinetic

(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 studies 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).[27, 28] 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 favourable 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”. Most patients with cluster headache have suicidal thoughts, but relatively little have self-harmful behaviour.[33]

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 VAS).[9]

Due to the high unmet need for new, effective, fast onset and better tolerated therapies for cluster headache, Lundbeck is planning to conduct a study in order to evaluate the long-term treatment with eptinezumab in patients with cluster headache. The study will evaluate, in an open-label design, the potential of eptinezumab to reduce the number of cluster headache attacks and severity of pain in a population of patients with cCH. The study will also provide supportive data to the ongoing Phase III study on the efficacy of eptinezumab in episodic cluster headache (19386A), to demonstrate that eptinezumab is a safe therapeutic option for cluster headache. The results from a Phase III study with galcanezumab in episodic cluster headache,[43] and its approval by the US FDA in this indication, prove the principle that mAbs, targeting CGRP, can be beneficial in cluster headache. Thus eptinezumab, which has similar biological properties and a faster onset of action in patients with migraine, is considered a viable therapeutic option to alleviate the symptoms of the disease in patients with cluster headache.

2 Objectives and Endpoints

The study objectives and endpoints are summarised in Panel 3.

Panel 3 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the long-term safety and tolerability of eptinezumab in patients with cCH	• Endpoints for the primary objective: – adverse events – absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values – potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values – development of specific anti-eptinezumab antibodies (ADA), including neutralizing antibodies (NAbs) – Columbia-Suicide Severity Rating Scale (C-SSRS) score

Secondary Objectives • To evaluate the efficacy of eptinezumab in patients with cCH	• Endpoints for the secondary objective (efficacy): – Conversion from cCH to episodic cluster headache (Week 0 to Week 48): Number of patients with no cluster headache attacks for ≥3 consecutive months (≥13 consecutive weeks) – Change from baseline in weekly number of times an abortive therapy (oxygen and/or triptans) was used (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Change from baseline in the average number of weekly attacks (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Change from baseline in the 5-point self-rating pain severity scale (calculated for each infusion with eptinezumab, taking the average across the first 4 weeks after the infusion) – Response: ≥30% reduction in number of weekly attacks (calculated for each infusion with eptinezumab, based on the average across the first 4 weeks after the infusion) – Response: ≥50% reduction in number of weekly attacks (calculated for each infusion with eptinezumab, based on the average across the first 4 weeks after the infusion) – cCH remission (Week 0 to Week 48): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks) – cCH remission (Week 0 to Week 12): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the first and second infusion) – cCH remission (Week 12 to Week 24): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the second and third infusion) – cCH remission (Week 24 to Week 36): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks between the third and fourth infusion) – cCH remission (Week 36 to Week 48): Number of patients with no cluster headache attacks for ≥1 month (5 consecutive weeks within the first 12 weeks after the fourth infusion) – Number of patients who received a transitional therapy during the Treatment Period (Week 0 to Week 48) – Patient Global Impression of Change (PGIC) score (assessed monthly after the first eptinezumab infusion) – Change from baseline in Sleep Impact Scale (SIS) domain scores (at each infusion and 4 weeks after each infusion)

Secondary Objectives (continued) • To evaluate the efficacy of eptinezumab in patients with cCH (continued)	• Exploratory endpoints for the secondary objective (efficacy): – Change from baseline in the average number of monthly attacks (per 4-week intervals after each eptinezumab infusion) – Change from baseline in the 5-point self-rating pain severity scale (taking the average across 4-week intervals after each eptinezumab infusion) – Response: ≥30% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Response: ≥50% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Response: 100% reduction in number of monthly attacks by 4-week intervals after each eptinezumab infusion, and for each of the periods between infusions with eptinezumab, and for 12 weeks after the last eptinezumab infusion – Change from baseline in monthly number of times an abortive therapy (oxygen and/or triptans) was used (per 4-week interval after each eptinezumab infusion)
• To evaluate the efficacy of eptinezumab on health-related quality of life, health care resource utilization, and work productivity	• Endpoints for the secondary objective: – Change from baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L) at Weeks 4, 16, 28, 40 and 48 – Health Care Resources Utilization (HCRU) at baseline, Weeks 4, 16, 28, 40 and 48 – Change from baseline in the Work Productivity Activity Impairment: General Health second version (WPAI:GH2.0) sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) at Weeks 4, 16, 28, 40 and 48
Exploratory Objective • To explore the target engagement of eptinezumab to CGRP	• Endpoint for the exploratory objective: – Change from baseline to each study time point in CGRP: CGRP-eptinezumab complex, free CGRP

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[34]

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

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[35] and applicable regulatory requirements.

An overview of the study design is presented in Panel 1.

The target population for this study is defined as patients with cCH, based on the IHS ICHD-3 classification,[4] with documented evidence of cCH prior to screening and confirmed via prospectively-collected information in the eDiary during the Screening Period.

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

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

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

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 eptinezumab 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 eptinezumab 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 last eptinezumab administration.

Eligibility will be assessed during the Screening Period and before the first administration of eptinezumab at Day 0 (Visit 2) as described in Panel 2.

The following visits will be site visits: Screening Visit at Week -4 (Visit 1), Investigational Medicinal Product (IMP) Visits at Weeks 0, 12, 24 and 36 (Visits 2, 5, 8 and 11), Completion Visit at Week 48 (Visit 14) and SFU Visit at Week 56 (Visit 15) or Withdrawal Visit, if applicable. All other study visits will be phone contact visits.

In exceptional situations to be approved by the Contract Research Organisation's (CRO) medical monitor, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and eptinezumab administration, while the remaining assessments (eDiary, electronic patient-reported outcomes [ePROs], C-SSRS, and investigator evaluations) can be conducted remotely as virtual clinic visits in line with the US FDA and European Medicines Agency (EMA) guidances.[36, 37]

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

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

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

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

Blood samples for exploratory eptinezumab quantification, and ADA and NAbs assessments will be collected at 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.

3.2 Rationale for the Study Design

The current study is planned as fixed-dose, multiple infusions study with an open-label design. The duration of the Treatment Period is chosen to allow generation of long-term exposure safety and tolerability data in patients with cCH, upon multiple infusions with eptinezumab 400 mg. The duration of the Screening Period is chosen to inform on the baseline disease activity in a population of patients with cCH who are managed according to the established standards of care.

The proposed study population are patients with cCH. Episodic cluster headache and cCH share common pathophysiology and overlapping clinical symptoms with the major differences between the two forms of cluster headache residing in the duration of the “active” and “remission” periods and, very important from a clinical point of view, patients with cCH have a very poor response to preventive medications.[38] The distinctions in two separate forms is, in some cases, solely virtual as when exacerbations lengthen, remissions shorten or more clusters occur than usual, the sufferers might be switching from episodic to chronic cluster headache.[39] Unhealthy lifestyle factors like smoking, alcohol overuse and high body mass index (BMI) are common for patients with episodic cluster headache and cCH and several

lifestyle related diseases like metabolic disease, gastric ulcer, menstrual diseases in women and visual disorders are being more frequently reported in cCH than in episodic cluster headache.[40] Therefore 1-year exposure to eptinezumab of patients with cCH, is considered an acceptable conservative approach to generate safety and tolerability data to adequately support the data, generated in the ongoing Phase III study in episodic cluster headache sufferers (19386A). In addition, the patients with cCH are the patient population, in need for long-term treatment to alleviate the symptoms of cluster headache.

As the current study will provide long-term safety data to support data from the ongoing Phase III study in episodic cluster headache sufferers (19386A), the same dose of 400 mg eptinezumab will be administered in both studies. This dose has been selected based on the fact that cluster headache patients have higher CGRP levels compared to migraine patients and healthy controls[24], and a higher frequency of attacks compared to patients with migraine, suggesting that a higher dose of eptinezumab compared to the dose(s) approved for migraine prevention, is needed to alleviate features of the disease, related to the CGRP pathobiology. This together with PK and safety data from the completed Phase I studies in the migraine program,[29] 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. This is in line with the dose considerations in the galcanezumab study in episodic cluster headache[43] which investigated the efficacy and safety of a dose which is almost three-folds the galcanezumab dose recommended for the treatment of migraine.[41, 42]

Fulfilment of criteria for cCH, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the screening period, that is CH attack frequency of minimum 14 CH attacks for the 28-day Screening Period. The lower 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.

Due to the high dose administered, the infusion time of eptinezumab is increased to 45 minutes in order to minimize the potential risk of hypersensitivity reactions associated with biologics.[44]

All patients will receive four infusions of eptinezumab 400 mg at 12-week intervals. Given the eptinezumab half-life and proven efficacy over 12 weeks in migraineurs, it is considered that all patients will be exposed to eptinezumab for a period of approximately 1 year. Abortive and preventive treatments, as well as transitional therapies are allowed, or allowed with restrictions, during the study, hence no patient will be denied access to standard treatments.

The sample size is chosen to support assessment of the safety and tolerability of long-term exposure to eptinezumab in patients with cluster headache. The number of patients treated will ensure that a sufficient number of patients will have been treated for 1 year, so the long-term exposure safety and tolerability of eptinezumab 400 mg can be assessed.[1]

The mean change from baseline in the number of cluster headache attacks is included to assess whether a symptom reduction is seen. This matches the primary endpoint from the ongoing placebo-controlled study in episodic cluster headache (19386A), which is the change from baseline in number of weekly attacks (Weeks 1–2), evaluated at Week 2. Secondary endpoints evaluating sleep disturbances, health-related quality of life, as well as work productivity, are included in the study to evaluate the treatment effect beyond the reduction in number of cluster headache attacks.

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.[43] 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 cCH. 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*[29] 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 treatment effect and safety of eptinezumab 400 mg is currently being investigated in patients with episodic cluster headache in an ongoing pivotal study (19386A).

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 12, 24, 36, 48 and 56 (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.[44] 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 will 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.

H. Lundbeck A/S considers the benefit-risk profile of Study 19385A to be acceptable based on the nonclinical and clinical data for eptinezumab.

4 Ethics

4.1 Ethical Rationale

This study will evaluate the long-term safety and tolerability of eptinezumab in patients with cCH.

The dose of 400 mg eptinezumab is selected, based on the fact that cluster headache patients have higher CGRP levels compared to migraine patients and healthy controls[24], suggesting that a higher dose of eptinezumab is needed to alleviate features of the disease, related to the CGRP pathobiology. The published results of the galcanezumab study in episodic cluster headache[43] 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.[41, 42]

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 eptinezumab 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 eptinezumab infusion and, at Weeks 12, 24, 36, 48 and 56 (SFU), and at Withdrawal Visit when applicable.

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 safe and effective treatment for episodic cluster headache.

In accordance with *Good Clinical Practice*,[35] qualified medical personnel at Lundbeck or the 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*,[35] 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).[45]

Risks Related to the Coronavirus Disease 2019

Lundbeck and the 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 guidances.[36, 37] 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 study in case of quarantine or lockdowns.
- Patient visits to site will be limited to seven on site visits over a time span of 60 weeks and all further contact will be conducted by phone. In exceptional situations to be approved by the CRO's medical monitor, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and eptinezumab administration, while the remaining assessments (eDiary, ePROs, C-SSRS, and investigator evaluations) can be conducted remotely via a virtual clinic visit. Consequently, this reduces the burden on the clinical 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 to allow for review and signature of *Informed Consent Form*(s) via virtual clinic visit and Screening Visit assessments may be extended over several days, if needed. For other visits, patients are allowed to complete 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 clinical site staff at a given visit.

- The percentage of onsite 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.

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' and CRAs' 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, 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 onsite 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 in line with the US FDA and EMA guidances.[36, 37]

Lundbeck and the 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 clinical site 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 onsite visits.

4.2 Informed Consent

No study-related procedures, including any screening 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 clinical site delegation log.

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

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

Depending of the country requirements, the number of ICFs may be different.

In case of pregnancy, and if required by local regulations, the patient and her partner will be asked to sign a separate *Informed Consent Form*. For country-specific pregnancy *Informed Consent Form*, refer to section 10.2.

Under exceptional circumstances, 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.[36, 37] 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.[37]

Re-screening of the Screening Visit is allowed under certain circumstances. Refer to section 8.2.3.

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. Vulnerable patients include pregnant and breastfeeding women, minors, patients that cannot read and understand the *Informed Consent Form(s)*, patients hospitalised without consent or deprived of liberty due to legal or administrative decision, as well as patients under legal guardianship and unable to provide their consent.

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 8.7);
- of the possibility to remain in the study even after treatment withdrawal (that is to attend all visits and perform all procedures except eptinezumab administration);
- of their right to request a copy of their personal data from the study via the investigator;
- 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 authorised by Lundbeck and authorised personnel from certain authorities (domestic, foreign, data protection agencies, or ethics committee [ECs] or Institutional Review Board [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 authorised 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* 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 gene expression profiling (ribonucleic acid [RNA]), metabolomic and proteomic analyses, including blood sampling for exploratory eptinezumab quantification, ADA biobanking and 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 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*.

A patient may, at any time and without stating a reason, specifically request the destruction of the patient's deoxyribonucleic acid (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[46] to ensure that requirements regarding personal data protection are met. If an external organisation will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck or delegate and the external organisation 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.

5 Study Population

5.1 Number of Patients and Regions

Planned regions:	Europe and North America
Planned number of screened patients (approximately):	200
Planned number of enrolled patients:	125

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 enrolled within the planned recruitment period.

The investigators will be notified immediately when the recruitment period comes to an end.

5.3 Selection Criteria

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

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

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. The patient is willing and able to attend study appointments within the specified time windows.

4. The patient is an outpatient.
5. The patient has adequate venous access for administration of study drug.
6. The patient has a diagnosis of cCH as defined by IHS ICHD-3 classification[4] (see section 9.1.2) with a history of cCH of at least 12 months prior to the Screening Visit.
7. The patient has a medical history of onset of cluster headache at ≤50 years of age.
8. The patient has an adequately documented record of previous abortive, transitional and preventive medication use for cCH, for at least 12 months prior to the Screening Visit.
9. The patient is able to distinguish cluster headache attacks from other headaches (such as tension-type headaches, migraine).
10. The patient has during the Screening Period, based on prospectively collected information in the eDiary, a cluster headache attack frequency of (*this requirement should not be shared with the patient*):
    - minimum 14 cluster headache attacks for the 28-day Screening Period
11. The patient has demonstrated compliance with the eDiary by entry of data for at least 24 out of 28 days during the 4-week Screening Period.
12. The patient is aged ≥18 and ≤75 years at the Screening Visit.
13. The patient, if a woman, must:
    - have had her last natural menstruation ≥12 months prior to the Screening Visit, OR
    - have been surgically sterilized prior to the Screening Visit, OR
    - have had a hysterectomy prior to the Screening Visit, 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:[*,47]
    - 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 the Screening Visit to ≥6 months after the last dose of eptinezumab.

[*] In line with the Clinical Trials Facilitation and Coordination Group's (CTFG) guidance document on "Recommendations related to contraception and pregnancy testing in clinical trials" (2020) and based on the available non-clinical and clinical data for eptinezumab, the risk of human teratogenicity/fetotoxicity for eptinezumab is considered unlikely. Therefore, in accordance with the CTFG guidance document, the use of at least an acceptable effective contraceptive measure is required for woman of child-bearing potential for a compound like eptinezumab and no contraception measures are needed for male patients.

14. The patient, if a woman of childbearing potential, must have a confirmed negative blood pregnancy test at the Screening Visit and a confirmed negative urine pregnancy test at the Baseline Visit.

Exclusion Criteria

1. The patient has previously been enrolled in this study and has received at least one eptinezumab infusion.
2. The patient has experienced failure on a previous treatment targeting the 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 the Screening Visit.
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 chronic paroxysmal hemicrania.
9. The patient has a history or diagnosis of chronic tension-type headache, 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 neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or longer than 1 hour).
10. Patients with a history of epilepsy.
11. Patients with a lifetime history of psychosis, bipolar mania, or dementia. 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 the Screening Visit.
12. The patient has a current diagnosis or history of substance abuse or alcohol abuse (Diagnostic and Statistical Manual of Mental Disorders, fifth edition [DSM-5®] criteria) <24 months prior to the Screening Visit.
13. The patient has any other disorder for which the treatment takes priority over treatment of cCH or is likely to interfere with study treatment or impair treatment compliance.
14. 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.
15. 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 eptinezumab. 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.

16. The patient has a history of clinically significant cardiovascular disease, including uncontrolled hypertension, vascular ischaemia or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
17. 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.
18. 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.
19. The patient has one or more clinically significant out-of-range vital signs at the Screening Visit.
20. The patient has a BMI $\geq$39 kg/m^2 at the Screening Visit.
21. The patient has been previously tested positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or Hepatitis C virus antibody (anti-HCV).
22. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
    - 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.
23. The patient has, at the Screening Visit, an abnormal ECG that is, in the investigator's opinion, clinically significant.
24. The patient is, at the Screening Visit or at the Baseline Visit, 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.
25. 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.
26. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
27. The patient is hospitalised without consent or deprived of liberty due to a legal or administrative decision.
28. The patient s under legal guardianship and unable to provide his consent.
29. The patient is not covered by the national mandatory health insurance plan (when applicable according to the country-specific law).

6 Investigational Medicinal Product

6.1 Treatment Regimen

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

6.2 Withdrawal Criteria

A patient must be withdrawn from the study if:

- the patient withdraws his or her consent (defined as a patient who **explicitly** takes back his or her consent); section 8.7 states how the patient's data will be handled;
- the patient has been enrolled 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.

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 interests of the patient that he or she be withdrawn from treatment;
- 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 re-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 ECG 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.

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

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 eptinezumab 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 eptinezumab 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 last eptinezumab administration.

6.3 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.

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

If the infusion is not completed or temporarily interrupted, the reason for the interruption must be recorded in the electronic case report form (eCRF) and in the patient's medical records. 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*.

6.4 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.

6.5 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. Assignment of IMP will be carried out in the IRT. Further information can be found in the *Pharmacy Manual*.

6.6 IMP Accountability

IMP accountability is documented in the IRT.

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.

7 Concomitant Medication

Concomitant medication is any medication other than eptinezumab that is taken during the study from up to 3 months prior to the Screening Visit until the SFU Visit.

The concomitant medications that are disallowed or allowed with restrictions during the study are summarised 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). Specific transitional and preventive treatments for cluster headache are allowed with restrictions (refer to list of therapies in Appendix II)

Details of all concomitant medication (prescription and over-the-counter) taken <3 months prior to the Screening Visit must be recorded in the eCRF at the first visit. 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.

If possible, a time window of at least 14 days should be allowed between COVID-19 vaccination and the Screening Visit. If the patient has recently received a COVID-19 vaccine, the investigator should judge if the patient can be administered eptinezumab infusion at the scheduled visit based upon the patient's individual response to the COVID-19 vaccine. As a precautionary measure, the COVID-19 vaccine should not be given within ±3 days of eptinezumab infusion.

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 "last" 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.

The study consists of a Screening Period (4 weeks), a Treatment Period (48 weeks), and a Safety Follow-up Period (8 weeks). After the Screening Period, the patient will attend the Baseline Visit (Day 0/Visit 2), which is the first visit of the Treatment Period. All patients will receive four IV infusions with eptinezumab 400 mg administered at 12-week intervals at Day 0 (Visit 2), at the end of Weeks 12 (Visit 5), 24 (Visit 8) and 36 (Visit 11). For all patients, who complete the study, a SFU Visit will be conducted 20 weeks (5 half-lives) after the last infusion of eptinezumab, that is at Week 56. For patients who withdraw from the study, the SFU Visit will be conducted 20 weeks (5 half-lives) after their last eptinezumab infusion.

The following visits will be site visits:

- Screening Visit at Week -4 (Visit 1)
- Baseline Visit at Week 0 (Day 0/Visit 2) – first eptinezumab infusion

- IMP Visits at Weeks 12, 24 and 36 (Visits 5, 8 and 11 - second, third, and fourth eptinezumab infusion)
- Completion Visit at Week 48 (Visit 14)
- SFU Visit at Week 56 (Visit 15)
- 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 SFU Visit, scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

All other study visits will be phone contact visits.

Patients will be given an eDiary at the Screening Visit (Visit 1, Week -4) and must be trained by the clinical site staff in its use and compliance requirements. Patients will complete eDiary entries daily during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40), and weekly for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48. Patients must complete the daily eDiary and ePRO entries prior to infusion and prior to any interaction with the clinical site staff. At each clinic visit and phone contact, a compliance check of the eDiary data will be conducted by the clinical site staff. In addition to the eDiary compliance checks performed at the defined study visits, ongoing evaluation of eDiary compliance will be performed by the clinical site (based on eDiary reporting) and more frequent contact with patients may be performed 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 2).

In exceptional situations to be approved by the CRO's medical monitor, site visits may only consist of blood and urine sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), ECG, vital signs, physical and neurological examinations, adverse events recording, and eptinezumab administration, while the remaining assessments (eDiary, ePROs, C-SSRS, and investigator evaluations) can be conducted remotely as virtual clinic visits in line with the US FDA and EMA guidances.[36, 37]

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

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

8.2 Screening Visit (Visit 1)

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

At the Screening Visit, the patient will be asked to sign the main *Informed Consent Form* and the *Informed Consent Form* for blood sampling for pharmacogenetics (optional). Depending of the country requirements, the number of ICFs may be different. Under exceptional circumstances, the discussion with the 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.[36, 37] According to 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.[37]

After the Screening Visit, a review of the data is required by the CRO medical monitor prior to the Baseline Visit (Day 0/Visit 2), to advise if the patient appears eligible and recommended to continue with the study procedures.

Re-screening for the Screening Visit is allowed according to criteria outlined in section 8.2.3.

For women of childbearing potential, a pregnancy test must be performed at the Screening Visit using serum beta-human chorionic gonadotropin (β-hCG). The investigator must check and document 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.

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

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

8.2.1 Pre-Screening

Each site must record in a pre-screening log which patients attended the Screening Visit.

8.2.2 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.

8.2.3 Re-Screening Visit

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

1. If the diagnosis of cCH as defined by IHS ICHD-3 classification[4] cannot be confirmed due to disease duration of less than 12 months during the maximum duration of the Screening Period, including the potential 1-week extension of this period granted by the CRO's medical monitor (Inclusion criterion N°8).
2. If the patient does not have during the Screening Period, based on prospectively-collected information in the eDiary, a cluster headache attack frequency of minimum 14 cluster headache attacks for the 28-day Screening Period (Inclusion criterion N°10).
3. If the patient has demonstrated poor compliance with the eDiary during the maximum duration of the Screening Period, including the potential 1-week extension of this period granted by the CRO's medical monitor, due to well documented reasons (sickness, travels, technical eDiary issues, or others) (Inclusion criterion N°11).
4. If the patient does not fulfil Exclusion criterion N°3 (previous participation in a clinical study <30 days or has taken any investigational products within 5 plasma half-lives (whichever is longer) prior to the Screening Visit.
5. If the patient does not fulfil Exclusion criterion N°18 (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.
6. Patients with uncontrolled high blood pressure at the Screening Visit (Exclusion criteria N°16 and 19): 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 the Re-Screening Visit.
7. Patients with a BMI ≥39 kg/m^2 (Exclusion criterion N°20).
8. A patient has answered "yes" to suicidal ideation questions 4 or 5 of the C-SSRS or "yes" to suicidal behaviour within the past month (Exclusion criterion N°24). 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 suicidal ideation questions 4 or 5 of the C-SSRS or "yes" to suicidal behaviour within the past 6 month, and are not considered by the investigator to be at significant risk for suicide.
9. For patients affected by COVID-19 during the Screening Period, that is 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's medical monitor.

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

The decision and the planning for re-screening must be based on a discussion between patients and investigators. Due to the short enrolment period, re-screening will only be possible if the study is still enrolling patients. Authorisation for re-screening may only be granted by the CRO's medical monitor after a thorough review of all data from the original Screening Visit.

The following information will also be recorded in the eCRF at the new Screening Visit:
- that the patient has previously been screened for the study;
- that re-screening has been authorised by the CRO's medical monitor;
- the screening number that was assigned to the patient at the original Screening Visit.

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

A patient may only be re-screened once.

8.2.4 Extension of Screening Period

Extension of the Screening Period is only allowed for patients with a *complete* Screening Visit and who fail to meet one or more of the following selection criteria:
1. If the patient does not have during the Screening Period, based on prospectively collected information in the eDiary, a cluster headache attack frequency of minimum 14 cluster headache attacks for the 28-day Screening Period (Inclusion criterion N°10).
2. If the patient has demonstrated poor compliance with the eDiary during the 4-week Screening Period due to well documented reasons (sickness, travels, technical eDiary issues, or others) (Inclusion criterion N°11).
3. If the patient does not fulfil Exclusion criterion N°18 (Disallowed medications or medications allowed with restrictions, refer to Appendix II) and the investigator considers that the criterion can be met by allowing additional 7 days in the Screening period.

In these cases, the Screening Period may be extended for a maximum of 7 additional days, and the eligibility of patients will be assessed on the last 28 days before baseline.

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

8.3 Baseline Visit (Day 0/Visit 2) + IMP infusion

The Baseline Visit (Day 0/Visit 2) also includes eptinezumab administration and will occur 4 weeks after the Screening Visit. Inclusion and exclusion criteria review must be done prior to dosing at the Baseline Visit (Day 0/Visit 2).

A blood sample for pharmacogenetics (optional) shall be taken prior to eptinezumab infusion.

For procedures preceding and following eptinezumab administration, see section 8.4.

8.4 IMP Visits (Visits 2, 5, 8 and 11) + IMP infusion

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

eDiary and ePRO must be completed prior to infusion and prior to any interaction with the clinical site staff. During the Treatment Period, ePROs which are scheduled in alignment with a clinic visit can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date.

A compliance check of eDiary data will be conducted by the clinical site staff and the patient will be assisted with re-training if necessary. In addition to the eDiary compliance checks performed at the defined study visits, ongoing evaluation of eDiary compliance will be performed by the clinical 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 eptinezumab infusion:

- Patients must complete the eDiary and ePROs. ePROs must be completed prior to blood and urine sampling.
- Vital signs must be assessed prior to blood sampling.
- The following assessments must be conducted: vital signs (including body temperature), weight, concomitant medications, adverse events, ECG, blood sampling (for clinical safety laboratory tests, exploratory eptinezumab quantification, ADA including NAb, and exploratory biomarkers), urine sampling (for clinical safety laboratory and pregnancy tests), physical and neurological examinations (if done at the discretion of the investigator), and C-SSRS administration.
- C-SSRS will be administered by the authorised rater at the clinic.

During eptinezumab infusion: Patients must be monitored for adverse events.

After end-of-eptinezumab-infusion, before the patient is discharged from the clinical site:

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

Blood samples for biobanking (gene expression profiling, and metabolomics/proteomics) shall be drawn prior to the first and the third eptinezumab infusion at Visits 2 and 8.

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.

8.5 Phone Contacts (Visits 3, 4, 6, 7, 9, 10, 12, 13)

The patient will be contacted via phone for eDiary compliance checks to ensure that selected ePROs assessments have been completed and for collection of relevant information such as adverse events and concomitant medication.

A compliance check of eDiary data will be conducted by the clinical site staff and the patient will be assisted with re-training if necessary. In addition to the eDiary compliance checks performed at the defined study visits, ongoing evaluation of eDiary compliance will be performed by the clinical 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 (Visits 3, 4, 6, 7, 9, 10, 12, 13), and SIS, EQ-5D-5L, HCRU, and WPAI:GH2.0 (Visits 3, 6, 9, 12). During the 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 3 days prior to the scheduled phone contact date.

Only the clinical 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 2).

8.6 Completion Visit (Visit 14)

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

Blood samples for biobanking (gene expression profiling, and metabolomics/proteomics) shall be drawn at the Completion Visit.

8.7 Withdrawal Visit

Three different scenarios can occur, depending on whether the patients withdraw from the study, from treatment or withdraw their consent.

Patients who withdraw from the study prior to the Completion Visit (Week 48/Visit 14), except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a further SFU Visit, scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

Patients who are withdrawn from the treatment prior to the Completion Visit (Week 48/Visit 14) 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 eptinezumab 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 last eptinezumab administration.

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

The reason for withdrawal must be recorded in the eCRF, and the investigator must ask specifically whether withdrawal was due to an adverse event.

For a patient who withdraws consent:

- if the patient withdraws consent during a site 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.

8.8 Safety Follow-up Visit (Visit 15)

The SFU Visit must be conducted as a visit to the clinical site. The SFU Visit should be conducted 20 weeks (5 half-lives) after the last eptinezumab administration.

The SFU Visit will be 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 after withdrawal, and a further SFU Visit, scheduled 20 weeks (5 half-lives) after the last eptinezumab administration.

For adverse events that were ongoing at the Completion/Withdrawal Visit and that resolved during the SFU 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. Serious adverse events (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.

8.9 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.

8.10 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 the Screening Visit (Week -4/Visit 1):

- Demographics (age, sex, race). Race will not be collected if restricted per local regulations
- Prior cCH documented history for review and documentation of previous treatment for cCH within 12 months prior to the Screening Visit (see section 12 for definition of adequately documented records)
- Other recent medication (past 3 months)
- Relevant history (social, medical, psychiatric, neurological)
- Substance use (e.g., smoking and alcohol consumption)
- Height
- Family history of cluster headache
- Urine drug screen
- Adverse events (serious and non-serious) present at Screening Visit must be collected, recorded, and reported to Lundbeck from the time the patient has signed the Informed Consent Form(s) at the Screening Visit
- Serum pregnancy test and collection of contraception measures (for women of childbearing potential)
- Blood and urine samples for clinical safety laboratory tests
- Vital signs (including body temperature), weight
- ECG
- Examinations (physical, neurological)
- C-SSRS
- eDiary/ePRO training
- eDiary recording

The following assessments will be performed at the Baseline Visit (before eptinezumab administration):

- Inclusion/exclusion criteria
- eDiary recording and ePROs
- Adverse events (serious and non-serious) must be collected, recorded, and reported to Lundbeck from the time the patient has signed the Informed Consent Form(s) at the Screening Visit
- Concomitant medication

- Urine pregnancy test (for women of childbearing potential)
- Blood and urine samples for clinical safety laboratory tests
- Blood samples for exploratory eptinezumab quantification, exploratory biomarkers, ADA including NAbs, and biobanking
- Blood samples for pharmacogenetics (optional)
- Vital signs (including body temperature), weight
- ECG
- Examinations (physical, neurological) at the discretion of the investigator
- C-SSRS
- eDiary compliance check

9.1.2 Diagnostic Assessments

IHS ICHD-3 guidelines[4] sections 3.1 and 3.1.2 for cCH are the diagnostic criteria to be used when assessing patient eligibility. Fulfilment of criteria for cCH according to the inclusion criteria in this protocol will be confirmed via prospectively-collected information in the eDiary during Screening Period, that is CH attack frequency of minimum 14 attacks during the 28-day Screening Period. The lower 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:

- 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 4 IHS ICHD-3 Guidelines for Chronic 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.

3.1.2 Chronic cluster headache

A. Attacks fulfilling criteria for 3.1 Cluster headache and criterion B below
B. Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year.

Chronic cluster headache may arise de novo (referred to as primary cCH) or evolve from episodic cluster headache (secondary cCH). In some patients change occurs from cCH to episodic cluster headache.[4]

9.1.3 Drug Screen

A urine drug screen will be performed at the central laboratory for the Screening Visit only. A positive result must be discussed with the CRO's medical monitor.

9.2 Efficacy Assessments

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

Patients will record cluster headache data on an eDiary from the Screening Period (Visit 1, Week -4) until the Completion Visit (Week 48/Visit 14):

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

Patients will complete the PGIC and SIS along with the pharmacoeconomic assessment ePROs (see section 9.3). It is preferable that 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:*
  - can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date. On the day of IMP Visits (Day 0/Visit 2, Week 12/Visit 5, Week 24/Visit 8, and Week 36/Visit 11), patients must complete the ePROs prior to infusion and prior to any interaction with the clinical site staff.
- *ePROs which are scheduled in alignment with a phone contact*:
  - must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled phone contact date.

9.2.1 Clinical Outcome Assessments

9.2.1.1 Use of Clinical Outcome Assessments Tools

The clinical outcome assessments (COA) tools are the eDiary and ePROs, guidance to patients on how to complete the tools will be given by designated clinical site 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/weekly cluster headache attacks, pain severity and medication use (that is the start and stop dates of cluster headache attacks and use of abortive cCH 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 the Screening Visit (or at the date of the first assessment if assessments are extended over several days), the patient will be assisted with the provisioning of the eDiary and will be trained in eDiary use and compliance requirements by designated clinical site staff. Patients will be instructed to complete the eDiary on a daily basis, during the Screening Period (from Week -4 to Day 0) and during the first 4 weeks that follow each eptinezumab infusion (Weeks 1 to 4, 13 to 16, 25 to 28, and 37 to 40), and on a weekly basis for Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48. The eDiary closeout 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 cCH (see section 9.1.2). The eDiary consists of applications and reports which will be used to derive the cluster headache endpoints and abortive medication use. The patient should record for each day/week 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/weekly information regarding the severity of pain associated to cluster headache and intake of cluster headache abortive medication. Cluster headache items will be assessed with a yes/no response; and severity of pain will be rated on an ordinal scale ranging from 0 to 4 (headache pain ratings: 0=none/barely any pain; 1=mild; 2=moderate; 3=severe; 4=excruciating).[48] Additional details regarding the questions that patients will answer can be found in the *eDiary Training Module*.

The Screening Visit will correspond to the day of eDiary distribution and will start the 28-day eDiary Screening Period. Any patient found to be ineligible for the study during Screening Period will not be enrolled. An *eDiary Eligibility Report* will be used to review baseline cluster headache attack days and eDiary compliance during the Screening Period for the eligibility assessment of:

- a minimum 14 cluster headache attacks for the first 28 days of Screening Period
- compliance by entry of cluster headache data for at least 24 out of the first 28 days of Screening Period.

On the Baseline Visit (Day 0/Visit 2), patients must ensure to complete eDiary recording of cluster headache attacks that ended prior to infusion (that is for cluster headache attacks which are ongoing or not yet recorded in the eDiary).

On each day during the first 4 weeks that follow each eptinezumab infusion, the patient will be asked to record eDiary data for the day. On Weeks 5 to 12, 17 to 24, 29 to 36, and 41 to 48, and until the Completion Visit (Week 48/Visit 14)/Withdrawal Visit, the patient will be asked to record eDiary data for the week.

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 the clinical site staff for review on a regular basis. At least 24 out of the first 28 days compliance is needed during the Screening Period. At each clinic visit and phone contact, a compliance check of eDiary will be conducted by the clinical site staff. Additionally, ongoing evaluation of eDiary compliance will be performed by the clinical 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

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 2) (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

The SIS[49] 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 on: daily activities (5 items); emotional well-being (4 items); emotional impact (4 items); energy/fatigue (5 items); social well-being (6 items); mental fatigue (3 items); and satisfaction with sleep (8 items). Each item, for 6 out of the 7 domains, is rated on a 5-point scale ranging from 1 ("always" or "all of the time") to 5 ("never" or "none of the time"), whereas satisfaction with sleep is rated on a 5-point scale ranging from 1 (very satisfied) to 5 (very dissatisfied). Each domain yields a score ranging from 0 to 100; items within each domain are summed and transformed using a formula. A higher score indicates 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 Clinical Outcome Assessments 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 Clinical Outcome Assessments Tool Training

The COA tools are patient-reported. Therefore, designated clinical 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). Clinical 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 clinical 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 authorised to train the patients on completion of the eDiary and ePROs in the study.

Documentation of training will be provided to the clinical site staff for archiving in the investigator site file and in the sponsor 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). It is preferable that 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:*
  - can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date. On the day of IMP Visits (Day 0/Visit 2, Week 12/Visit 5, Week 24/Visit 8, and Week 36/Visit 11), patients must complete the ePROs prior to infusion and prior to any interaction with the clinical site staff.
- *ePROs which are scheduled in alignment with a phone contact*:
  - must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled phone contact date.

9.3.1 Clinical Outcome Assessments

9.3.1.1 Use of Clinical Outcome Assessments 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

The EQ-5D-5L[50] is a patient-reported assessment designed to measure the patient's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a 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

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 study.

9.3.1.4 Work Productivity and Activity Impairment: General Health Second Version

The WPAI:GH2.0[51] 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 Clinical Outcome Assessments 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).

9.3.1.6 Clinical Outcome Assessments Training

The COA tools are patient-reported. Therefore, designated clinical 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). Clinical 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 clinical 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 authorised to train the patients on completion of the eDiary and ePROs in the study.

Documentation of training will be provided to the clinical site staff for archiving in the investigator site file and in the sponsor TMF.

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

9.4 Pharmacokinetic Assessments (Blood Sampling for Exploratory Eptinezumab Quantification)

The blood samples (maximum total volume: 10.5 mL per patient) for exploratory eptinezumab quantification in plasma will be drawn in accordance with Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The bioanalysis will be performed by a contracted laboratory under the responsibility of Bioanalysis - Biologics, H. Lundbeck A/S, according to a protocol approved by Lundbeck.

The results will be subjected to a pharmacokinetic analysis, that will be reported separately.

9.5 Pharmacodynamic Assessments (Exploratory Biomarkers)

Blood samples (maximum total volume 36 mL) for the pharmacodynamic/exploratory biomarkers including 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 the Screening Visit when the patient signs the *Informed Consent Form(s)*. 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 eptinezumab. 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.

At IMP Visits, adverse events are monitored prior to, during, and after infusion.

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 5.

Panel 5 Clinical Safety Laboratory Tests

Haematology	**Liver**[b]	**Infection**[c]
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]	S-C-reactive protein [CRP] **Immune response lab kit**[c] P-histamine [HISTAMINE] S-tryptase [TRYPTASE] immunoglobulin E [IgE] complement C3, C4 [C3 and C4]
Electrolytes[b]	**Kidney**[b]	**Urine**[f]
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[c]
Endocrine and Metabolic[b]	**Lipids**[b,d]	**Pregnancy**[g]
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[h] [HCG] Urine (dipstick)
B = blood; P = plasma; S = serum; U = urine		

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

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

The blood and urine 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 the Baseline Visit. 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. In this case, these results will be recorded in the eCRF together with the local laboratory reference ranges.

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 eptinezumab). A patient with a value that is out-of-range at the Completion Visit (Week 48/Visit 14) 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 SFU 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.

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

9.6.4 Height and Weight

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

The patients will be weighed wearing light clothing and no shoes. A similar amount of clothing must be worn on each occasion. At IMP Visits, weight is assessed prior to infusion.

9.6.5 Electrocardiograms

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 QT_c intervals.

The ECG printout must be evaluated and signed by the investigator prior to eptinezumab administration. The investigator has the final decision on the interpretation of the ECG results.

9.6.6 Physical and Neurological Examinations

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

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's designee must be properly trained and have experience in performing these examinations. 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.

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.[52] 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 to 10 minutes to administer and rate the C-SSRS.

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

The C-SSRS is a paper and pencil measure that should only be administered by a qualified rater and the investigator review must be documented in the patient's medical records. 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 authorised to administer the C-SSRS in the study. Documentation of training and certification will be provided to raters for archiving in the investigator site file and in the sponsor 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 clinical site in a *C-SSRS Guideline.*

9.6.8 Anti-Drug Antibody including Neutralizing Antibody Assessments

Blood samples for ADA, including NAb assessments (maximum total volume 15 mL), will be collected in accordance with Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual.*

The serum samples will be analysed by a contracted laboratory under the responsibility of Department of Bioanalysis - Biologics, H. Lundbeck A/S, according to a protocol approved by Lundbeck.

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 research study, that may help to increase our understanding of the aetiology of neurological diseases, such as migraine and the molecular basis of the drug response.

Although the potential future exploratory analyses will help to increase our understanding of the aetiology of cCH 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 and disease are currently not characterized to a level that translates to a meaningful clinical advantage, individual results from the exploratory analyses will 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 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 biomarker analysis will be double-coded, that is one code key will be stored at the clinical 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 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) 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 Brooks Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by the 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 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 Brooks Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by the 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 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 Brooks Life Sciences, Indianapolis, IN, USA) for storage. Sample preparation and analysis may be performed by the CRO or by a bona fide research collaborator.

The genetic variants to be analysed may include single nucleotide polymorphisms and copy number variations. The analytical methods may be polymerase chain reaction (PCR), quantitative PCR, 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 accordance with Panel 2. The maximum volume of blood to be collected during the study for this purpose will be 15 mL.

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

9.8 Order of Assessments

At each IMP Visit (Day 0/Visit 2, Week12/Visit 5, Week 24/Visit 8, Week 36/Visit 11), **prior** to eptinezumab infusion:

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

At each IMP Visit (Day 0/Visit 2, Week12/Visit 5, Week 24/Visit 8, Week 36/Visit 11), **during** eptinezumab infusion: patients must be monitored for adverse events.

At each IMP Visit (Day 0/Visit 2, Week12/Visit 5, Week 24/Visit 8, Week 36/Visit 11), **after** end-of-eptinezumab-infusion, before the patient is discharged from the clinical site:

- Patients must be monitored for at least 1 hour.
- The following assessments must be conducted: vital signs including body temperature, and the patient must be monitored for adverse events. Vital signs must be assessed prior to blood sampling.
- A blood sample for exploratory 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:*
  - can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date. On the day of IMP Visits (Day 0/Visit 2, Week 12/Visit 5, Week 24/Visit 8, and Week 36/Visit 11), patients must complete the ePROs prior to infusion and prior to any interaction with the clinical site staff.
- *ePROs which are scheduled in alignment with a phone contact*:
  - must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled phone contact date.
- It is preferable that 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 221.5 mL during the study.

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

After analysis, all remaining serum or plasma samples will be stored at -20°C for a minimum of one year. Whole blood and urine sediment samples will be stored for a minimum of one week. The central laboratory will be notified by Lundbeck when the biological samples may be destroyed.

The biobank blood samples and any derived material for potential future exploratory gene expression profiling, metabolic or proteomic biomarker analyses, or ADA assessments will be destroyed ≤10 years after the end of the study (see definition in section 8.10).

9.10 Treatment Compliance

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

Anyone administering eptinezumab 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[53]

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 the *Informed Consent Form(s)* at the Screening Visit until the Safety Follow-up Visit.

Serious adverse event – 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 hospitalisation or prolongation of existing hospitalisation
- 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 hospitalisation, 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 hospitalisation; or development of drug dependency or drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the *Informed Consent Form(s)* 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*[29]), and related to a medicinal product by either the investigator or Lundbeck.

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

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

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 judgement 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 eptinezumab infusion, as assessed by the investigator, the infusion must be discontinued immediately (see section 6.2) and appropriate therapy instituted. Any events believed to be allergic reactions should be discussed with the medical monitor.

The clinical 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 serum 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.

Once completed, *Pregnancy Form* (paper) shall be sent to:

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

If sent by email, the investigator must ensure that the *Pregnancy Form* is sent password protected and that the password is sent in a separate email.

An uncomplicated pregnancy should not be reported as a SAE; hospitalisation for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with a 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 occurs on the day of eptinezumab administration); intensity; causal relationship to eptinezumab; action taken; and outcome. If the adverse event is not related to eptinezumab, 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

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

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

When Rave is available again, the site must enter the SAE information into Rave.

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*[54], 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 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 SFU Visit, whichever comes first. At the SFU Visit, information on new adverse events, 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 SFU Visit must be handled in the same manner as SAEs that occur during the study considering relation to IMP. 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 48/Visit 14) 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 SFU 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 6.2) 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 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 the 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, organised 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

All electronic data will be transferred by the designated 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
- Eptinezumab quantification results

11.2 Retention of Study Documents at the Clinical 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 clinical site will be provided with all data related to the clinical site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the clinical 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 site file 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 clinical site.

If off-site storage is used, a study-specific binder will remain at the clinical site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator site file and must be kept in a secure place by the clinical site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator Site File 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.

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 clinical site. The document will also list which data may be recorded directly on the eCRFs.

Only patients with cCH 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 clinical 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 cCH diagnosis and previous acute medication use for cCH, covering a period of at least 12 months prior to the Screening Visit and general medical history prior to the study. Information about changes in the patient's medical history, treatment for cCH and other concomitant medication that might occur between the Screening Visit and the Baseline Visit 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 clinical 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 clinical site's recruitment rate, and the compliance of the clinical 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.

Due to COVID-19, if the clinical site is closed to the CRO's monitor for safety measures, remote source data verification may be done in exceptional cases, if allowed per local and site regulations.

13 Audits and Inspections

Authorised 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 numbers will appear on these copies.

Patient data will not be disclosed to unauthorised 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 studies sponsored by Lundbeck or competitors.

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

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-enrolled set* (APES) - all-patients-enrolled
- *all-patients-treated set* (APTS) - all patients in the APES who receive infusion with eptinezumab
- *full-analysis set* (FAS) - all patients in the APTS who have a valid assessment of the baseline number of monthly attacks and a post-baseline assessment of number of monthly attacks

The safety and tolerability analyses, and the exposure, disposition, and demographics and baseline characteristics will be based on the APTS. The efficacy analyses will be based on the FAS.

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.

16.4 Patient Disposition

Patient disposition will be summarised and include the number of patients in the APTS who completed or withdrew from treatment, as well as the number of patients in each analysis set (APES, APTS, and FAS).

The number of patients who withdrew from the study will be summarised by primary reason for withdrawal 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 summarised by visit.

16.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name by visit.

16.7 Exposure and Compliance

Exposure and compliance will be calculated per patient and summarised by visit.

The number of patients infused and patients who had their infusion interrupted will be summarised by visit. Patients whose infusion took more than 60 minutes and patients who had their infusion interrupted will be listed with period, infusion start date/time and end date/time, and reasons if any.

16.8 Efficacy Analyses

16.8.1 General Efficacy Analysis Methodology

All confidence intervals (CIs) will be 95% CIs, unless otherwise specified.

Baseline number of weekly attacks will be derived from eDiary data collected in the Screening Period (Week -4 to Day 0).

16.8.2 Analysis of the Secondary Endpoints

Details on derivations and imputations of eDiary data (daily or weekly data entries), as well as sub-group analyses, will be described in the *Statistical Analysis Plan* (SAP).

For continuous endpoints, descriptive statistics for absolute values and change from baseline when appropriate will be provided by visit. In addition, continuous endpoints will be

modelled using mixed models for repeated measurements (MMRM) including baseline score, visit and baseline interacting with visit, if applicable.

The estimated means, standard errors and CIs will be provided by visit. For response variables the counts, percentages and CI will be presented by visit.

16.8.3 Testing Strategy

No formal testing will be done.

16.9 Safety Analyses

The primary objective of the study is to evaluate the long-term safety and tolerability of eptinezumab in patients with cCH. This will be evaluated based on the collected data on adverse events, vital signs, weight, ECGs, clinical safety laboratory test values, C-SSRS, ADA and NAbs.

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(s)* and prior to the date of first dose of eptinezumab
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity during or after administration of the first dose of eptinezumab

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarised for the full study and by 3-month periods.

Allocation of TEAEs to Study Periods

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

16.9.2 Analysis of Other Safety Endpoints

Absolute values and change from baseline for vital signs, weight, ECGs, clinical safety laboratory test values will be summarised by visit. The number of patients exceeding the PCS values will be tabulated. The incidence, kinetics and magnitude of ADA and NAb response(s) will be evaluated.

16.10 Interim Analyses

No interim analysis is planned.

16.11 Sample Size and Power

In line with the ICH E1 guideline,[1] the study aims at providing data in 100 patients exposed to eptinezumab for 1 year. Dodick (2020),[2] in patients suffering from cCH included in a 12-week study, reports less than 4% withdrawals. In the European Union Drug Regulating Authorities Clinical Trials (EudraCT) report for study NCT02964338,[3] in patients suffering from cCH, approximately 7% of patients dropped out from the first 12-week period; the withdrawals due to the "sponsor terminated study" are not included as a reason for withdrawal. As the withdrawal rate for a long-term study like the current study is unknown, 125 patients are planned to be enrolled and treated, allowing for 100 patients to complete, with a withdrawal rate of 20%. The withdrawal rate will be monitored during the study conduct, and if a clear deviation from the assumed withdrawal rate is observed, the number of patients enrolled and treated might be increased to ensure that data is available for a sufficient number of patients with long-term exposure.

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.

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 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).[55]

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 clinical 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 will be provided to the clinical 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 Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	Interventional, open-label, fixed-dose multiple administration study to evaluate long-term treatment with eptinezumab in patients with chronic cluster headache
Study No.:	19385A
Edition No.:	2.0
Date of edition:	25 November 2021

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 Medical Safety:	PPD

Authorisation

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.
Anticonvulsants	• Anticonvulsants can only be used for preventive treatment for cluster headache and are allowed with restrictions- see *Cluster Headache Therapies.*

Cluster Headache Therapies	• **Abortive treatment** The following abortive therapies for cluster headache attack are allowed at any time during the study: – High-flow oxygen; – Oral triptans, sumatriptan subcutaneous injection; sumatriptan nasal spray; zolmitriptan nasal spray; – Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs); – Dihydroergotamine (allowed for not more than 3 times per week) or ergot derivatives; – Octreotide. – Opioids are allowed with restrictions (maximum 2 days per week). – Cannabinoids are allowed if prescribed or if locally approved • **Transitional treatment** Disallowed for 30 days prior to the Screening Visit and during the Screening Period: – Greater occipital nerve block; – Injected and oral steroids (used for headache treatment). • **Preventive treatment:** Stable dose (with restriction on the maximum dose for lithium only) for 1 month prior to the Screening Visit and during the Screening Period: – Verapamil; – Topiramate; – Gabapentin; – Valproate; – Candesartan; – Lithium: the maximum dose must be as per the country-specific guidelines for management of patients with CH **AND** the se-lithium level must be below the toxic serum level of lithium, based on the reference ranges of the local laboratory; – Indomethacin. Initiation, discontinuation, and change of dose are allowed during the Treatment Period and the SFU Period. At any time: – Melatonin Initiation, discontinuation, and dose modifications are allowed during the Treatment Period and the SFU Period. Dihydroergotamine is disallowed for use as a preventive treatment. • **Other treatment and interventions:** Disallowed for 4 months prior to the Screening Visit and until the SFU Visit: – Botulinum toxin type A or B, 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 Visit and until the SFU Visit:

Drug Class	Details
	– 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 the Screening Visit.
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 and remains stable until the Completion Visit (Week 48).
Cannabinoids	Allowed with restrictions- see *Cluster Headache Therapies.*
COVID-19 vaccine	Allowed with restrictions: • If possible, COVID-19 vaccine should not be administered <14 days prior to the Screening Visit. • If possible, COVID-19 vaccine should not be given within ±3 days of eptinezumab infusion.
Ergot alkaloids	• Methergine is disallowed for 14 days prior to the Screening Visit and until the SFU Visit. Other medications in the same class are allowed.
Steroids: Oral and Injectable	Allowed with restrictions: • *For transitional treatment for CH,* see *Cluster Headache Therapies* • For indications other than cluster headache: i. Disallowed during the Screening Period ii. Short-term treatment (maximum 3 days, followed by potential tapering) is allowed from Baseline until the SFU Visit
Illicit substances	Disallowed for 2 months prior to the Screening Visit and until the SFU Visit: Psilocybin (mushrooms), lysergic acid diethylamide (LSD), or 2-bromo-LSD, or other illegal drugs.