Clinical Study Protocol

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

Eptinezumab

Study No.:	18898A
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Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 18898A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Eptinezumab
Study Title Interventional, randomized, double-blind, parallel-group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments	
Objectives and Endpoints	
Objectives	**Endpoints**
Primary Objective • To evaluate the efficacy of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments	• Primary endpoint: – Change from baseline in the number of monthly migraine days (Weeks 1-12) • Key secondary endpoints: – Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 1-12) – Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 1-12) – Change from baseline in the number of monthly migraine days (Weeks 13-24) • Secondary endpoints: – Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 13-24) – Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 13-24) – Response: patients with 100% reduction from baseline in monthly migraine days (Weeks 1-12) – Response: patients with 50% reduction from baseline in monthly headache days (Weeks 1-12) – Response: patients with 75% reduction from baseline in monthly headache days (Weeks 1-12) – Response: patients with 100% reduction from baseline in monthly headache days (Weeks 1-12) – Change from baseline in the number of monthly headache days (Weeks 1-12) – Migraine/headaches with severe pain intensity (Weeks 1-12) – Change from baseline in the number of monthly migraine days with use of acute medication (Weeks 1- 12) – Change from baseline in number of monthly migraine days with use of acute medication (Weeks 13-24) – Patient Global Impression of Change (PGIC) score at Week 12 – PGIC score at Week 24

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

Objectives and Endpoints (continued) Objectives	Endpoints
	– Change from baseline in the HIT-6 score (at Weeks 36, 48, 60, and 72) • <u>Exploratory endpoints:</u> – Response: patients with 100% reduction from baseline in monthly migraine days – Response: patients with 50% reduction from baseline in monthly headache days – Response: patients with 75% reduction from baseline in monthly headache days – Response: patients with 100% reduction from baseline in monthly headache days – Migraine/headaches with severe pain intensity – Change from baseline in the number of monthly migraine days with use of acute medication – PGIC score – Change from baseline in the number of monthly migraine days in patients with MOH – Patients with a migraine on the day after first dosing – Change from baseline in MBS score – Change from baseline in monthly number of Migraine attacks for each 12-week period – Change from baseline in monthly number of Headache episodes for each 12-week period – Change from baseline in the MSQ v2.1 sub-scores – Change from baseline in the EQ-5D-5L VAS score – Change from baseline in HCRU – Change from baseline in WPAI sub-scores
Safety Objective • To evaluate the safety and tolerability of eptinezumab • To evaluate the long-term safety and tolerability of eptinezumab	• <u>Safety Endpoints</u> – Adverse events – Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values – Potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values – Development of specific anti-eptinezumab antibodies (ADA) including neutralizing antibodies (NAbs) – Columbia-Suicide Severity Rating Scale (C-SSRS) score

Study Methodology

- This is an interventional, multi-national, multi-site, randomized, double-blind, placebo-controlled Phase IIIb study designed to demonstrate efficacy and safety of eptinezumab for migraine prevention in patients with unsuccessful prior preventive treatments. The placebo-controlled period will be followed by an extension period where all patients will receive active treatment to assess the long-term safety, tolerability and effect of eptinezumab.
- The total study duration from the Screening Visit to the Completion Visit is approximately 76 weeks and includes a Screening Period (28-30 days), Placebo-controlled Period (24 weeks) and Extension Period (48 weeks).
- The target population for this study is defined as patients with chronic migraine (CM) or episodic migraine (EM), as outlined in the IHS ICHD-3 guidelines,[1] and with documented evidence of failure to 2-4 different preventive migraine medications in the past 10 years. The aim is that approximately 40% of the randomized patients are patients with EM.
- 840 patients will be randomly allocated via a randomization system to one of three treatment groups: eptinezumab 300 mg, eptinezumab 100 mg, or placebo, in a ratio of 1:1:1.
- Randomization will be stratified by monthly headache days (MHDs) at baseline (≤14 MHDs/ >14 MHDs) and by country.
- The patient will receive IMP starting from the Baseline Visit to follow a Q12W dosing schedule (every 12 weeks) with either eptinezumab or placebo by IV infusion over 30 minutes (+15 minutes).
- At Visit 8 patients will enter the Extension Period. Patients who were assigned to placebo in the Placebo-controlled Period will be randomly allocated to one of two treatment groups: eptinezumab 300 mg or eptinezumab 100 mg with a ratio of 1:1. Patients assigned to eptinezumab 300 mg or eptinezumab 100 mg in the Placebo-controlled Period will continue on their original assignments.
- Patients will complete a daily headache eDiary from the time of screening until the Completion/Withdrawal Visit.
- During infusion visits, assessments of safety will be performed before and after each infusion. At these visits, AEs will be collected as well as safety laboratory tests, ECG, weight, and vital signs. Patient-reported outcomes (PROs) must be administered prior to infusion.
- Patients who complete the study will attend a Completion Visit which will include a Safety Follow-up evaluation at 12 weeks after their last dose of IMP.
- Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit 12 weeks after their last dose of IMP and undergo Safety Follow-Up evaluations. Patients who withdraw prior to the Week 24 Visit will additionally undergo Efficacy Follow-Up evaluations.
- An independent Safety Data Monitoring Committee (DMC) will regularly monitor the patients' safety data according to the *DMC Charter*.
- In general, no information about individual treatment codes will be available to investigators, patients or site-facing CRO personnel until after all patients have completed the study.
- The results of the Placebo-controlled Period will be reported when ended for all patients. All data from the Placebo-controlled Period will be cleaned and the database for the Placebo-controlled Period will be locked. Data will be unblinded for the reporting team (Sponsor), and all analyses specified in the SAP for data collected in the Placebo-controlled Period will be performed and included in the Clinical Study Report (CSR). After all patients have completed the study, an addendum to the CSR, including the results from the Extension Period, will be produced. Investigators and patients will be informed about which treatment (active or placebo) their patients received in the Placebo-controlled Period and the actual dose of eptinezumab received in the Extension period only after the last patient has completed the study.
- *Assessments performed in a subset of patients:*
  - Exit interviews will be performed shortly (no later than 2 weeks) after the last assessment of the Week 24 Visit or Withdrawal Visit (for patients who withdraw prior to Week 24) on a subset of patients (hereafter referred to as the '*Exit Interview subset*') after all visit assessments are completed. The aim is to complete exit interviews for 100 patients out of the first 345 randomized patients.
- The study design is presented in Panel 1 and the scheduled study procedures and assessments are summarized in Panel 2.

Number of Patients Planned

840 patients, recruited from specialist settings are planned for randomization: 280 patients in the eptinezumab 300 mg group, 280 patients in the eptinezumab 100 mg group and 280 patients in the placebo group.

Target Patient Population

Main Inclusion Criteria

- The patient has a diagnosis of migraine as defined by IHS ICHD-3 guidelines with a history of chronic or episodic migraines of at least 12 months prior to the Screening Visit.
- The patient has a migraine onset of ≤50 years of age.
- The patient has ≥4 migraine days per month for each month within the past 3 months prior to the Screening Visit.
- The patient has demonstrated compliance with the Headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit.
- The patient fulfils the following criteria for CM or EM in prospectively collected information in the eDiary during the screening period:
  - For patients with CM: Migraine occurring on ≥8 days and headache occurring on >14 days
  - For patients with EM: Migraine occurring on ≥4 days and headache occurring on ≤14 days
- (a) The patient has documented evidence of treatment failure* (must be supported by medical record or by physician's confirmation specific to each treatment) in the past 10 years of 2-4 different migraine preventive medications out of the following:
  - propranolol/metoprolol
  - topiramate
  - amitriptyline
  - flunarizine
  - candesartan
  - valproate/divalproex
  - botulinum toxin A/B (if documented that botulinum toxin was taken for chronic migraine)

  AND

  (b) The patient has failed two of the below of which at least one must be due to inadequate efficacy:
  - propranolol/metoprolol
  - topiramate
  - amitriptyline
  - flunarizine
  - candesartan
- The patient has a history of either previous or active use of triptans for migraine.
- 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 calcitonin gene-related peptide (CGRP) pathway.
- The patient has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications.

* Treatment failure could have been due to inadequate efficacy (that is, no clinically meaningful improvement at the locally recommended dose for at least 3 months) and/or safety/tolerability reasons (that is, discontinuation due to adverse events) and/or contraindications (that is, ineligibility due to medical reasons). Treatment failure corresponds to the first documented failure for each medication.

Target Patient Population (continued)

- The patient has confounding and clinically significant pain syndromes, (for example, fibromyalgia, chronic low back pain, complex regional pain syndrome).
- The patient has a diagnosis of acute or active temporomandibular disorder.
- The patient has a history or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine, and migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
- The patient has a psychiatric condition that is uncontrolled and/or untreated for a minimum of 6 months prior to the Screening Visit. Patients with a lifetime history of psychosis and/or mania in the last 5 years prior to the Screening Visit are excluded.
- The patient has a history of clinically significant cardiovascular disease or vascular ischaemia or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
- The following recent and concomitant medications are disallowed or allowed with restrictions with respect to their use prior to or during the study (the list is not comprehensive):
- Disallowed: any investigational products within 30 days or 5 plasma half-lives (whichever is longer) before the Screening Visit; eptinezumab or other monoclonal antibody treatment targeting the CGRP pathway; preventive migraine treatments; oral anti-CGRPs for acute treatment; CNS- and migraine-related devices (neuromodulation, neurostimulation) or injectable therapy (trigger point injections, extracranial nerve blocks, or facet joint injections); botulinum toxin; monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, or nimesulide.
- Allowed with restriction: prescription or over-the-counter medication for acute treatment of migraine prescribed or recommended by a healthcare professional; hormonal therapy (for example, contraceptives, hormone replacement therapy); anti-impotence agents; barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital); prescription opiates (including single-ingredient or combination medications containing opiates, opioids, tramadol, or tapentadol), and non-pharmacological interventions (including CBT).

Investigational Medicinal Product, Doses and Mode of Administration

- Eptinezumab – 100 or 300 mg, Concentrate for Solution for Infusion 100 mg/ml added to 100 mL of 0.9% normal saline, intravenously
- Placebo – 100 mL of 0.9% normal saline, intravenously

The IMP will be administered by intravenous infusion over 30 minutes (+15 minutes), once every 12 weeks.

Assessment Details

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

eDiary

Patients will complete a daily headache eDiary from the time of screening until the Completion/Withdrawal Visit consisting of applications and reports which will be used to derive the migraine and headache endpoints. The eDiary will be distributed to each subject at the Screening Visit after subject training on eDiary use by site staff. The eDiary data from the 28 days following the Screening Visit will be used to determine eligibility criteria, baseline migraine and headache values and eDiary compliance. At the relevant study visits, compliance data from the eDiary will be reviewed at the study site.

Headache Impact Test (HIT-6)

The HIT-6 (v1.0) is a Likert-type, self-reporting questionnaire designed to assess the impact of an occurring headache and its effect on the ability to function normally in daily life. The HIT-6 contains 6 questions, each item rated from “never” to “always” with the following response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. The total score for the HIT-6 is the sum of each response score and ranges from 36 to 78. The life impact derived from the total score is described as followed: Severe (≥60), Substantial (56-59), Some (50-55), Little to None (≤49). It takes less than 5 minutes to complete the HIT-6 questionnaire.

Assessment Details (continued)

Most Bothersome Symptom

The Investigator will verbally obtain the most bothersome symptom associated with the patient's migraines during the Baseline Visit. Patients will be asked to rate the improvement in this symptom from baseline on a 7-point scale identical to the scale used for the PGIC. The MBS areas include: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, other. It takes less than 5 minutes to complete the MBS.

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

The MSQ v2.1 is a patient-reported outcome designed to assess the quality of life in patients with migraine. It consists of 14 items covering three domains: role function restrictive; role function preventive; and emotional function. Each item is scored on a 6-point scale ranging from 1 (none of the time) to 6 (all of the time). Scores are obtained for each domain and ranges from 0-100. Higher scores indicate better quality of life. It takes approximately 5-10 minutes to complete the MSQ v2.1.

Health Care Resource Utilization (HCRU)

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

Exit interview (applies to Exit Interview subset)

Exit interviews will be conducted on patients, tailored to the target population and this trial to help better understand experiences with disease, gain additional insight into trial data, support interpretation of quantitative assessments and endpoints to discuss meaningfulness of change.

Statistical Methodology

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

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

The patients and data will be classified into the analysis sets according to these definitions at separate Classification Meetings. For the reporting of the Placebo-controlled Period, the Classification meeting will be held after the data base release for the reporting of the Placebo-controlled Period but before the blind has been broken and will concern the classification into APTS and FAS. For the addendum to CSR, the Classification meeting will be held after the data base release for the reporting of the Extension Period and will concern the classification into APTS_LT and FAS_LT.

If not otherwise stated, tables, figures and listings (TFLs) in the Placebo-controlled Period will be summarized by randomized treatment group and TFLs in the Extension Period will be summarized by treatment group in the extension (eptinezumab 300 mg or 100 mg).

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

Demographics and Baseline characteristics will be based on FAS, and safety tables (including exposure and medications) will be based on APTS in the Placebo-controlled Period, and on FAS_LT and APTS_LT respectively in the Extension Period.

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

Statistical Methodology (continued)

- Primary analysis of the primary endpoint:
  - The number of monthly migraine days (MMDs) Week 1-12 summarises diary data across Weeks 1 to 12. Details on derivation and imputations of days with missing or incomplete eDiary data will be described in the SAP. Changes from baseline in MMDs at the 6 first 4-week intervals will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The analysis will be performed using all available monthly change scores for the first 6 months in the study. The model will include the following fixed effects: month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, and Weeks 21-24), country, stratification factor (MHDs at baseline: ≤14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction. An unstructured variance structure will be used to model the within-patient errors. The mean differences between each dose of eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-visit interaction in the MMRM model. The primary comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 1-12.
- Analysis of the key secondary endpoints:
  - For the key secondary endpoints based on response rates, treatment effects compared to placebo will be analyzed using logistic regression. The model will include baseline MMDs as a continuous covariate, and treatment and stratification (MHDs at baseline: ≤14 />14) as factors.
  - The change from baseline in HIT-6 score for the Placebo-controlled Period will be analysed using a mixed model repeated measures (MMRM) including baseline HIT score as covariate, treatment, country, stratification factor (MHDs at baseline: ≤14 />14), and week as fixed factors. In addition, the model will include treatment-by-week interaction, baseline HIT-6 score-by-week interaction, and stratum-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Treatment effects will be calculated based on least squares means for the treatment-by-week interaction estimated at Week 12.
  - Change from baseline in the number of MMDs (Weeks 13-24), will be analysed using the same MMRM methodology as for the primary endpoint. The comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 13-24.
- Sensitivity analyses of the primary endpoint:
  - The impact of missing data in the derivation of the primary endpoint (days with missing or incomplete information in the eDiary) will be evaluated by applying different methods of imputation.
- Sensitivity analyses of the key secondary endpoints:
  - endpoints where data imputation is used, the impact of the imputations will be assessed in sensitivity analyses, applying different methods of imputation.
- Secondary endpoints:
  - Analyses of continuous data based on diary data will use a similar model to the primary analysis, and continuous scale endpoints will be analysed by the same MMRM methodology as for HIT-6. Response variables will use similar analyses as the key secondary response endpoints. The endpoints; patients with a migraine on the day after first dosing and 100% responders for MMDs and MHDs (Weeks 1-12) will be analysed using an extended Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factor (MHDs at baseline: ≤14 />14).

Testing Strategy

The testing strategy will be a sequence of tests, either testing one endpoint at a time or using Bonferroni-Holm to test a group of endpoints. Only if one step has shown a statistically significant effect will the formal testing continue with the next step, thus ensuring protection of the type 1 error.

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

Step1

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

Testing Strategy (continued)

Step 2

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

Step 3

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

Step 4

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

Step 5

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

Step 6

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

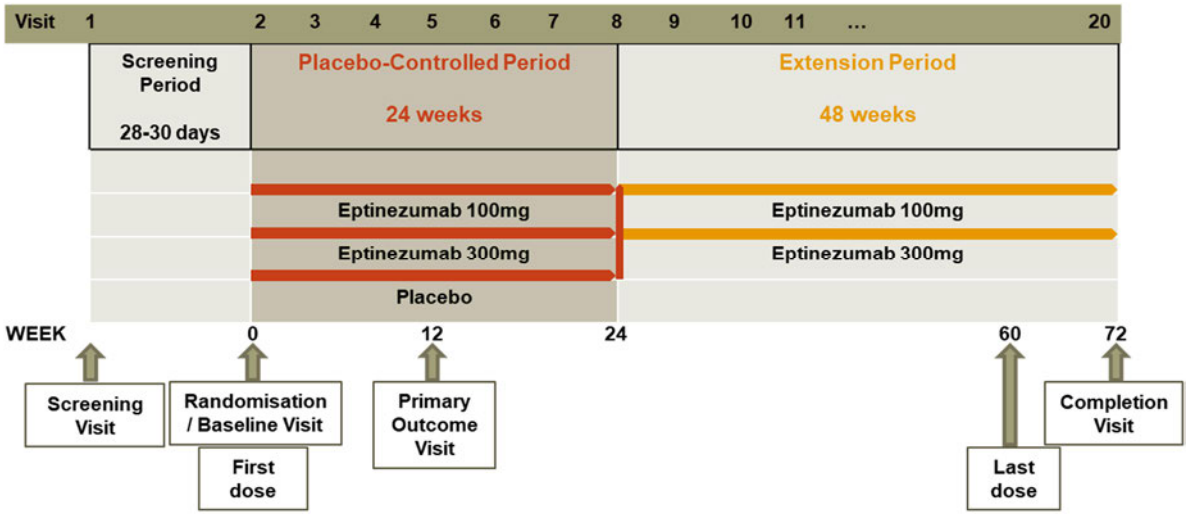
Sample Size Considerations

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

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

The power was determined by simulating the testing strategy (10000 simulations) assuming normal distributions with similar mean and SD for continuous endpoints and similar success rates as the response variables in the Phase III studies for the corresponding population (EM or CM) without assuming the variables to be correlated. With 280 patients per treatment group, assuming that 40% of the patients will be from the EM population and 60% from the CM population, and that 2% of the patients do not have a post-baseline assessment of the primary endpoint, simulations show that the power for the test of the primary endpoint is approximately 94% for the comparison of 100 mg to placebo and 99% power for the comparison of 300 mg to placebo. The individual key secondary endpoints had a power of at least 68% for showing an effect, with a combined power of 58% for seeing an effect for all primary and key secondary endpoints and both doses in the testing strategy.

Panel 1 Study Design



The study consists of a Screening Period and a Placebo-controlled Period. IMP (eptinezumab 100 mg, eptinezumab 300 mg, or Placebo) is administered by intravenous infusion every 12 weeks, starting at the Baseline Visit. Patients completing the 24-week Placebo-controlled Period will enter an Extension Period where all patients will receive eptinezumab once every 12 weeks.

Panel 2 Study Procedures and Assessments

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

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

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

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

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

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

b If the date of a clinic visit or phone contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit.

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

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

e Dosing must occur at the Baseline Visit.

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

g Assessments involving interviews and scales must be done before the infusions. All efficacy and pharmacoeconomic assessments are PROs. PROs which are scheduled in alignment with a clinic visit can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date. Additionally, PGIC (at Week 4 only), HIT-6, EQ-5D-5L, HCRU, WPAI which are scheduled in alignment with a phone contact must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled phone contact date.

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

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

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

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

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

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

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

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

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

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

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

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

t Pregnancy test at Screening to be performed using serum β-HCG. At all other visits, urine pregnancy testing will be performed and in case of a positive finding, confirmatory testing will be performed via serum β-HCG.

u Exit Interview subset: Patients undergoing the exit interviews must provide signed subset-specific Informed Consent. The exit interview will be conducted shortly (no later than 2 weeks) after the last assessment of the Week 24 Visit or Withdrawal Visit for patients who withdraw prior to Week 24. The exit interview must be conducted after all visit assessments are completed. Details will be provided in a separate exit interview guide.

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

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

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

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

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

β-hCG	beta-human chorionic gonadotropin
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS_LT	all-patients-treated long-term set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
Bpm	beats per minute
BSC	best supportive care
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CNV	copy number variation
CRA	clinical research associate
CRF	case report form
CRO	clinical research organisation
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EM	episodic migraine
EMA	European Medicines Agency
EQ-5D-5L	Euroqol 5 Dimensions
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FAS_LT	full-analysis long-term set

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCRU	health care resource utilization
HCV	hepatitis C virus
HDL	high density lipoprotein
HIT-6	headache impact test
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	institutional review board
IRR	infusion related reactions
IRT	interactive response technology
IV	intravenous
LDL	low density lipoprotein
Lu	Lundbeck
MBS	most bothersome symptom
MHDs	monthly headache days
MMDs	monthly migraine days
MMRM	mixed model for repeated measurements
MOH	medication overuse headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire Version 2.1
NA	not applicable
NAb	neutralizing antibody
OC	observed case(s)
PCR	polymerase chain reaction
PCS	potentially clinically significant
PGIC	patient global impression of change
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
Q12W	every 12 weeks
QP	qualified person
qPCR	quantitative polymerase chain reaction
QRS	specific ECG interval describing ventricular depolarization

QT	specific ECG interval describing ventricular depolarization/repolarization
QT_c	heart-rate corrected QT interval
QT_{cF}	heart-rate corrected QT interval using Fridericia's correction formula
RNA	ribonucleic acid
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical software package from the SAS® Institute
SD	standard deviation
SNP	single-nucleotide polymorphism
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
TMF	trial master file
TNC	trigeminal nucleus caudalis
TSH	thyroid stimulating hormone
WPAI	Work Productivity and Activity Impairment

Major Changes Since Last Edition

The following summarizes the major changes since the last edition of this Clinical Study Protocol. The changes are made to align with study-specific documents developed after the finalisation of the protocol, for consistency and alignment across sections, or to reflect the changes to implement for the remainder of the study. Minor wording clarifications/edits are also made but not included in the list below.

General:

Text and panels related to the interim analysis are deleted throughout the protocol as Sponsor decision was taken to cancel the interim analysis and inform sites as per memo *18898A Interim Analysis* (dated 03-Mar-2021).

Text is added throughout the protocol to clarify that only those patients who withdraw prior to Week 24 will undergo Exit Interview. This is done for consistency and alignment across sections.

Text about requirement for eDiary data review is deleted throughout the protocol, as site staff are not required to conduct a review of eDiary data at each study visit.

In addition, the following changes have been implemented:

Chapter/Section Number	Section Title	Change
Synopsis	Study Methodology	*Updated*: Bullet 5 – to align with the update under 3.1 *Overview of the Study Design* (bullet 1) – see below.
Synopsis	Target Patient Population	*Updated: Inclusion Criteria* bullet 4 – to align with the update under 5.3 *Selection Criteria (Inclusion Criterion 9)* – see below.
Synopsis	Assessment Details	*Updated:* To align with the update under 9.2.4 *Most Bothersome Symptom (MBS)* – see below.
Panel 2	Screening and Baseline Procedures and Assessments	*Updated:* To align with the update under 9.1.1 *Demographics and Baseline Characteristics* – see below.
Panel 2	Footnotes	*Updated:* • Footnote a: text related to 'requirement of screening assessments prior to the Baseline Visit' is deleted for clarification purposes. • Footnote t: clarifying text related to 'serum testing for pregnancy' is added to align with the *Laboratory Services Agreement* (version 1.0, dated 31-Mar-2020) effective at study start. • Footnote u: to align with the information in section 9.5.1 *Exit Interview (subset).* • Footnote y: to align with the assessments ticked in Panel 2.

Chapter/Section Number	Section Title	Change
Chapter 3	3.1 Overview of the Study Design	*Updated*: • Country is added as a stratification factor to align with the *Randomization Specification* (signed 12-Dec-2019) and *Endpoint IRT Specification* (version 1.0, dated 11-Feb-2020). Both documents were effective at study start. • Sponsor is deleted from list of personnel who are without access to information on individual treatment codes during the study. Following the data-base lock for the Placebo-controlled Period, Sponsor personnel involved in the review of the CSR were unblinded to individual treatment codes.
Chapter 3	3.2 Rationale for the Study Design	*Added:* Clarifying text to explain: • the definitions of EM or CM (number of migraine and headache days) according to the eligibility criteria. • that patients with concurrent Medication Overuse Headache were allowed to be included in the study as aligned with the eCRF (effective at study start). • the capture of aura occurrence and migraine medication for qualifying a migraine day in the eDiary.
Chapter 5	5.3 Selection Criteria	*Updated:* • Inclusion Criterion 9: clarification is made that the 28-day screening period was calculated relative to the Screening Visit date (and not the randomization date) as aligned with the *Project Design Specification* (version 1.0, effective at study start). • Inclusion Criteria 9 and 10: reference is added to the definitions explained in new section 9.1.3 *Classifications for Eligibility* – see below. • Inclusion Criterion 14: updated to align with the Clinical Trials Facilitation and Coordination Group (CTFG) guidance to loosen the requirements for contraception during study conduct. Update applies after enrolment was completed and after completion of the Placebo-controlled Period. • Exclusion Criterion 4: clarifying text is added (*has taken any investigational drug within*) to align with Appendix II. *Deleted:* • Inclusion Criterion 15: to align with the CTFG guidance to remove the requirements for contraception during study conduct. Update applies after enrolment was completed and after completion of the Placebo-controlled Period.
Chapter 7	7.2 Use of Coronavirus Disease 2019 Vaccine	*Added:* New section regarding use of the COVID-19 vaccine as per memo *18898A COVID-19 Vaccine Guidance* (dated 26-Mar-2021) which was provided to sites.
Chapter 8	8.1 Overview	*Updated:* Text related to *'requirement of screening assessments prior to the Baseline Visit'* is deleted for clarification purposes. *Added:* New text to explain that headache data from the eDiary will be made available during the study to site staff for the remainder of the study.
Chapter 8	8.2 Screening Visit (Visit 1)	*Added:* Clarifying text to align with the main master *Informed Consent Form* (version 3.0, dated 27-May-2020) to explain that some patients were invited to attend up to two Screening Visits to complete all assessments at screening.

Chapter/Section Number	Section Title	Change
Chapter 8	8.2.3 Re-screening	*Added:* Text to explain that rescreening was allowed for patients being in quarantine due to a positive COVID-19 test as per memo *18898A COVID-19 Extension of the Screening Visit or Rescreening* (dated 05-Nov-2020) which was provided to sites.
Chapter 8	8.8 Unscheduled Visit	*Added:* Clarifying section to explain when an unscheduled visit can occur and which assessments can be performed, as aligned with the eCRF (effective at study start).
Chapter 9	9.1.1 Demographics and Baseline Characteristics	*Updated:* Smoking and alcohol consumption is corrected to substance use and moved from Screening to Baseline Visit in Panel 2. This is to reflect the collection of other substance use during the Screening Period as aligned with the eCRF (effective at study start).
Chapter 9	9.1.2 Diagnostic Assessments	*Deleted:* Definition of a migraine day as a corrected definition is added to new section 9.1.3 – see below.
Chapter 9	9.1.3 Classifications for Eligibility	*Added:* New section to explain the definitions of a migraine day, headache day and eDiary compliant day (linked to inclusion criteria 9 and 10) applied when the patients were enrolled in the study. Definitions are aligned with the eligibility algorithm in the *Project Design Specification* (version 1.0, effective at study start).
Chapter 9	9.1.4 Definitions for Baseline Disease Activity and Analysis	*Added:* New section to explain the definitions applied for calculation of number of EM/CM patients (and low/high frequency EM patients) for subgroup analyses. Definitions are based on IHS guidelines[42] and are aligned with the *Statistical Analysis Plan* (version 2, dated 13-Oct-2021).
Chapter 9	9.2 Efficacy Assessments	*Added:* Sentence added about PRO completion for consistency and alignment with other sections (8.5 *IMP Visits,* 9.3 *Pharmacoeconomic Assessments,* 9.7 *Order of Assessments*). Aligned with the *Project Design Specification* (version 1.0, effective at study start).
Chapter 9	9.2.2 eDiary	*Deleted:* Text for missed completion of eDiary is deleted as it is not in alignment with the *Project Design Specification* (version 1.0, effective at study start).
Chapter 9	9.2.3 Patient Global Impression of Change (PGIC)	*Updated:* Numerical representation of PGIC scoring is corrected to align with the coding of the responses done for similar clinical outcome assessments in other studies and to align with the *Statistical Analysis Plan* (version 2, dated 13-Oct-2021).
Chapter 9	9.2.4 Most Bothersome Symptom (MBS)	*Updated:* Text is corrected to indicate that patient will rate improvement in the symptom from baseline (and not screening) to align with Panel 2 and the *Project Design Specification* (version 1.0, effective at study start). *Updated:* Text is corrected to include additional symptoms (mental cloudiness, fatigue, pain with activity, mood changes, other) to align with the eCOA specifications in the Project Design Specification (effective at study start).
Chapter 9	Panel 5	*Updated:* Clarifying text is added to footnotes to align with the *Laboratory Services Agreement* (version 1.0, dated 31-Mar-2020) effective at study start. This applies to the requirement for reflex testing for TSH, confirmatory testing for serology, microscopic evaluation for urine and serum testing for pregnancy.

Chapter/Section Number	Section Title	Change
Chapter 9	9.6.3 Blood Sampling for Metabolomic and/or Proteomics	*Updated:* Gene expression profiling is corrected to metabolomic and/or proteomics.
Chapter 10	10.2 Pregnancy	*Updated:* Text regarding partner pregnancy is removed as there is no longer requirement to collect data on pregnancies for female partners of male study subjects in eptinezumab studies.
Chapter 12	Monitoring Procedure	*Deleted:* Text regarding collection of medical history for the prior 3 months is removed to align with eCRF (effective at study start). *Updated:* Clarifying text is added for acceptable documented evidence of previous treatment failures to reflect the requirements when the patients were enrolled in the study. *Added:* Text to explain that remote source data verification may be conducted by CRA in accordance with local and national regulations if on-site visits are not possible.
Chapter 16	16.9.1 Analysis of Adverse Events	*Updated:* Clarifying text is added that the TEAE applies during or after administration of IMP.
Appendix II	Vaccinations	*Added:* COVID-19 vaccine guidance is added as per memo *18898A COVID-19 Vaccine Guidance* (dated 26-Mar-2021) which was provided to sites.

1 Introduction

1.1 Background

1.1.1 Overview

Migraine is a disabling disorder characterised by headache and often accompanied by nausea, vomiting, photophobia, and phonophobia.[1] Attacks of migraine typically last between 4 and 72 hours, produce significant disability, and recur often without warning, over decades of time. Migraine is more common in women and most prevalent through the 3rd and 4th decades of life, amplifying its impact on family and career development.[2] Migraine is one of the most prevalent neurological disease for which medical treatment is sought, and worldwide, is considered the leading cause of disability for people under the age of 50 and 2nd leading cause of disability worldwide.[3,4] Generally, migraine begins as an episodic disease. Between attacks of migraine, the nervous system returns to a normal (premorbid) state of function. However, approximately 2.5% of people with episodic migraine will annually transform from episodic to chronic migraine, meaning they are experiencing migraine on greater than 15 days per month for at least 3 consecutive months.[5,6,7]

Currently pharmacological treatments of migraine include acute treatments and preventive medications. Preventive treatments are used on a sustained basis for periods of months to years to prevent migraine from occurring. Preventive drug treatment may be appropriate in a number of instances, including where frequency of attacks per month is two or higher, or where a patient's quality of life is severely impaired.[8] Conventional preventive medications belong to different pharmacological categories (for example, beta blockers, anticonvulsants) and were all initially developed for other conditions. These treatments show little efficacy and often poor tolerability in patients with migraine, resulting in frequent early discontinuation of treatment.[2,9,10,11,12,13,14] Thus, there is a substantial proportion of patients who do not respond to, or cannot tolerate, existing treatments and there is a need for preventive medications which are more effective and better tolerated than the current standard of care.[15]

Calcitonin gene-related peptide (CGRP) is thought to play an important role in migraine by facilitating the transmission of migraine pain, thereby contributing to the induction of the pronociceptive stage through modulation of the central nervous system (CNS).[16,17] Studies in animals and humans indicate that the trigeminal ganglion and the trigeminal nucleus caudalis (TNC) are likely to be sites of action of CGRP in migraine. In addition, CGRP is expressed in many locations within the CNS, including regions that may be relevant to migraine pain.[18,19] During migraine attacks, there is an increase in the plasma levels of CGRP in the external jugular vein.[20] In addition, IV infusion of CGRP has caused migraine and headache in patients with migraine, suggesting that the increase in CGRP observed during spontaneous migraine attacks plays a causative role.[21] CGRP dilates intracranial and extracranial blood vessels, and regulates mast cell degranulation, that during migraine, leads to the secretion of vasoactive, proinflammatory, and neurosensitizing mediators, thereby contributing to migraine pathogenesis.[22,23]

A large body of evidence has established the CGRP pathway as a potential target for the treatment of migraine. Studies with monoclonal antibodies targeting CGRP or the CGRP receptor have shown that inhibition of CGRP is efficacious in the treatment of CM and EM.[24] Further recent trials with these agents have shown good efficacy and tolerability in patients who experienced previous failure of 2 to 4 different pharmacological migraine preventive medications.[25,26]

Eptinezumab (Lu AG09221) is a humanised monoclonal antibody that inhibits the action of CGRP. It is in development by H. Lundbeck A/S for the preventive treatment of migraine. Results from two pivotal, placebo-controlled, Phase III trials showed that eptinezumab led to significant reductions in monthly migraine days in patients with episodic or chronic migraine (ALD403-CLIN-006 and ALD403-CLIN-011).[27,28] Unique to eptinezumab's profile is that it is administered as an intravenous infusion and throughout its Phase II and Phase III development programs, it has consistently demonstrated preventive efficacy as soon as the first day following infusion and has potential for a sustained benefit over the 12-week dosing cycle. Eptinezumab is currently being reviewed by the Food and Drug Administration (FDA) for an indication in migraine prevention.

The following sections 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

Several primary pharmacodynamic animal studies (rats, rabbits and cynomolgus monkeys) have demonstrated the ability of eptinezumab to block CGRP-driven neurogenic dermal vasodilation[30] in a generally dose dependent manner with doses of eptinezumab as low as 0.1 mg/kg.

Furthermore, 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. In these studies, eptinezumab induced no functional effects upon the CNS or renal system in rats or monkeys, or upon the cardiovascular or respiratory (excluding the 6-month study) systems in monkeys.

Eptinezumab is not expected to interact directly with deoxyribonucleic acid (DNA) or other chromosomal materials, and genotoxicity assessments have not been performed. The carcinogenic potential for eptinezumab has not been thoroughly investigated based upon an extensive evaluation of the literature related to inhibition of CGRP, angiogenesis, and tumor growth, as well as the absence of eptinezumab-related proliferative findings in long term studies in cynomolgus monkeys or clinical trials.

Eptinezumab is being developed for the prophylaxis of migraine, and a significant proportion of migraineurs are women of childbearing potential.[31] Given the patient population, and in conformance with applicable guidance documents, a complete package of reproductive/development toxicity studies was conducted. In these studies, administration of

eptinezumab by intravenous injection to pregnant female rats or rabbits at 75 or 150 mg/kg/dose was well tolerated and there were no maternal effects or evidence of embryofetal mortality (embryolethality), alterations in growth (fetotoxicity) or structural abnormalities (teratogenicity) for either species.

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

1.1.3 Clinical Data

The clinical program of eptinezumab is composed of 5 completed studies to date; 4 studies are placebo-controlled (Phase Ib study in frequent EM (ALD403-CLIN-002),[32] Phase II study in CM (ALD403-CLIN-005),[33] PIII study in frequent EM (ALD403-CLIN-006),[27] PIII study in CM (ALD403-CLIN-011)[28] and 1 study is open-label (PIII study in CM (ALD403-CLIN-013)).[34,35] Another study (ALD403-CLIN-015)[36] is ongoing to assess treatment of eptinezumab in patients experiencing an acute attack of migraine.

Results from the two pivotal, placebo-controlled, Phase III trials showed that eptinezumab at doses of 100 mg or 300 mg administered by IV infusion every 12 weeks (2 infusions) led to significant reductions in monthly migraine days in patients with episodic or chronic migraine (ALD403-CLIN-006 and ALD403-CLIN-011).[27] 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. Eptinezumab is currently being reviewed by the FDA for an indication in migraine prevention.

In the completed eptinezumab clinical studies, the most common adverse reaction in ≥2% of treated patients and ≥2% of placebo patients were nasopharyngitis. The majority of these adverse events were categorized as mild to moderate. The safety of eptinezumab has been evaluated in 2,076 patients with migraine who received at least one dose of eptinezumab, representing 1615 patient-years of exposure. Long term data with eptinezumab is limited; however, 128 subjects have been treated with up to 2 years of exposure and no new significant findings have been identified during the long-term follow-up.

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

1.2 Rationale for the Study

There is a substantial proportion of patients who do not respond to, or cannot tolerate, existing treatments and there is a need for preventive medications which are more effective and better tolerated than the current standard of care.[15]

The demonstrated efficacy and tolerability profile of eptinezumab supports its use as a potential therapeutic candidate for patients who failed prior preventive treatment for CM and EM. Unique to eptinezumab's profile is that it is administered as an intravenous infusion and, throughout its Phase II and Phase III development programs, it has consistently demonstrated preventive efficacy as soon as the first day following infusion and has potential for a sustained benefit over the 12-week dosing cycle.

Thus the current study will evaluate the efficacy and tolerability of eptinezumab in this target population and provide evidence-based treatment guidance for these patients with difficult-to-treat migraine. The onset of the preventive effect will be explored specifically with early timepoints. Additionally, endpoints evaluating health-related quality of life, including most bothersome symptoms, as well as work productivity, are included in the study to demonstrate the impact of preventive treatment beyond the reduction in pain and migraine days. The preventive effect will be studied over a treatment duration of 24 weeks and the extension period will allow further investigation of the long-term safety and efficacy profile of eptinezumab.

2 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 3.

Panel 3 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments	• Primary endpoint: – Change from baseline in the number of monthly migraine days (Weeks 1-12) • Key secondary endpoints: – Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 1-12) – Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 1-12) – Change from baseline in the number of monthly migraine days (Weeks 13-24) • Secondary endpoints: – Response: patients with 50% reduction from baseline in monthly migraine days (Weeks 13-24)

Objectives	Endpoints
	– Response: patients with 75% reduction from baseline in monthly migraine days (Weeks 13-24) – Response: patients with 100% reduction from baseline in monthly migraine days (Weeks 1-12) – Response: patients with 50% reduction from baseline in monthly headache days (Weeks 1-12) – Response: patients with 75% reduction from baseline in monthly headache days (Weeks 1-12) – Response: patients with 100% reduction from baseline in monthly headache days (Weeks 1-12) – Change from baseline in the number of monthly headache days (Weeks 1-12) – Migraine/headaches with severe pain intensity (Weeks 1- 12) – Change from baseline in the number of monthly migraine days with use of acute medication (Weeks 1- 12) – Change from baseline in number of monthly migraine days with use of acute medication (Weeks 13-24) – Patient Global Impression of Change (PGIC) score at Week 12 – PGIC score at Week 24 – Change from baseline in the number of monthly migraine days in patients with Medication Overuse Headache (MOH) (Weeks 1-12) – Patients with a migraine on the day after first dosing – Change from baseline to Week 12 in Most Bothersome Symptom (MBS) score • <u>Exploratory endpoints:</u> – Change from baseline in the number of monthly headache attacks for each 12-week period – Change from baseline in the number of monthly migraine attacks for each 12-week period

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

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

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the Declaration of Helsinki.[37]

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

This study will be conducted in compliance with the protocol, Good Clinical Practice,[38] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

840 patients, recruited from specialist settings are planned for randomization: 280 patients in the eptinezumab 300 mg group, 280 patients in the eptinezumab 100 mg group and 280 patients in the placebo group.

The target population for this study is defined as patients diagnosed with chronic migraine (CM) or episodic migraine (EM), as outlined in the IHS ICHD-3 guidelines,[1] and with documented evidence of failure to 2-4 different preventive migraine medications in the past

10 years (see section 9.1.1). The aim is that approximately 40% of the randomized patients are patients with EM.

Patients will be randomly allocated via a randomization system to one of three treatment groups: eptinezumab 300 mg, eptinezumab 100 mg, or placebo, in a ratio of 1:1:1. Randomization will be stratified by monthly headache days (MHDs) at baseline (≤14 MHDs/ >14 MHDs) and by country.

The total study duration from the Screening Visit to the Completion Visit is approximately 76 weeks and includes a Screening Period (28-30 days), Placebo-controlled Period (24 weeks) and Extension Period (48 weeks). The patient will receive IMP starting from the Baseline Visit to follow a Q12W dosing schedule (every 12 weeks) with either eptinezumab or placebo by IV infusion over 30 minutes (+15 minutes).

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

Patients will be assigned a headache eDiary at the Screening Visit and will be required to complete this daily from the time of screening until the Completion/Withdrawal Visit. During infusion visits, assessments of safety will be performed before and after each infusion. At these visits, AEs will be collected as well as safety laboratory tests, ECG, weight, and vital signs. Patient-reported outcomes (PROs) must be completed prior to infusion.

Patients who complete the study will attend a Completion Visit which will include a Safety Follow-up evaluation at 12 weeks after their last dose of IMP.

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

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.

An independent Safety Data Monitoring Committee (DMC) will regularly monitor the patients' safety data according to the DMC Charter.

In general, no information about individual treatment codes will be available to investigators patients or site-facing CRO personnel (blinded team) until after the last patient has completed the study.

The results of the Placebo-controlled Period will be reported on when ended for all patients. All data from the Placebo-controlled Period will be cleaned and the database for the Placebo-controlled Period will be locked. Data will be unblinded for the reporting team (Sponsor) and

all analyses specified in the SAP for data collected in the Placebo-controlled Period will be performed and included in the Clinical Study Report (CSR). After all patients have completed the study, an addendum to the CSR, including the results from the Extension Period, will be produced. Investigators and patients will be informed about which treatment (active or placebo) their patients received in the Placebo-controlled Period and the actual dose of eptinezumab received in the Extension period only after the last patient has completed the study.

Assessments performed in a subset of patients:

Exit interviews will be performed shortly (no later than 2 weeks) after the last assessment of the Week 24 Visit or Withdrawal Visit (for patients who withdraw prior to Week 24) on a subset of patients (hereafter referred to as the '*Exit Interview subset*') after all visit assessments are completed. The aim is to complete exit interviews for 100 patients out of the first 345 randomized patients.

3.2 Rationale for the Study Design

The current study includes a 24-week double-blind, randomized placebo-controlled period to investigate whether eptinezumab can lead to clinically significant improvement in patients with unsuccessful prior preventive treatments. The primary endpoint is the change in the number of monthly migraine days and will be evaluated at Week 12 as this is expected (on the basis of Phase III data) to be an adequate duration to investigate the efficacy of eptinezumab. Additionally, endpoints will be evaluated at Week 24 to investigate if the relative efficacy is sustained in this difficult-to-treat population. The extended period beyond Week 12 will also allow adequate time to investigate a beneficial effect on quality of life and on potential reduction in new migraine attacks, after a reduction in the number of monthly migraine days is observed. A 48-week dose-blinded Extension Period with eptinezumab treatment is included to enable further investigation on the long-term safety and efficacy and for further insights into the effectiveness profile of eptinezumab. Endpoints evaluating health-related quality of life, including most bothersome symptoms, as well as work productivity, are included in the study to demonstrate the impact of preventive treatment beyond the reduction in pain and migraine days.

The study population is selected on the basis that there is a substantial proportion of patients who do not respond to, or cannot tolerate, existing treatments and there is a need for preventive medications which are more effective and better tolerated than the current standard of care.[15] Thus the study will include patients with EM or CM in whom 2 to 4 migraine preventive medications of different pharmacological class were previously unsuccessful.

The proposed study population are patients with EM (migraine occurring on ≥4 days and headache occurring on ≤14 days) or CM (migraine occurring on ≥8 days and headache occurring on >14 days), which reflect the commonly used definitions of EM and CM patients. This target population corresponds to the patient populations in the completed phase III studies in EM (ALD403-CLIN-006) and CM (ALD403-CLIN-011)[27,28] and in which eptinezumab demonstrated efficacy and consequently justifies the patient population for this

study. Fulfilment of criteria for EM or CM, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the Screening Period. Amongst patients with CM, there is a proportion of patients with concurrent Medication Overuse Headache (MoH).[39,40] These patients are allowed to be included in the study.

During the study, the patients will be asked about occurrence of aura in the eDiary. To minimize patient burden during the study for migraine with aura, the patient's usual aura will only be described and diagnosed at the Screening Visit. Subsequently, the patient will be asked about occurrence of aura in the eDiary based on a question in the eDiary; *"Have you experienced aura with this headache?"* Patients will be asked in the eDiary to fill in if they took any medications to treat a headache and if so, if they took this medication because they believed this was a migraine. As several medications are used both to treat non-migraine-headache and migraine, the classification of a migraine-specific medication is not feasible by registering the product used alone. Furthermore, the intention is to avoid that, for example, a mild tension-type headache that was treated with paracetamol is counted as a migraine day.

The placebo group is representative of the best supportive care (BSC) as the study allows acute treatment of migraine when prior preventive treatments have not worked. Thus, the study will compare the efficacy of eptinezumab and BSC versus BSC alone.

Doses of 100 and 300 mg eptinezumab administered by IV infusion every 12 weeks have shown to be efficacious and to generally be well tolerated in the treatment of EM and CM in the Phase III studies. Thus, these doses and dosing interval are recommended for the target population in this study.

The sample size of 840 patients for the primary endpoint is based on the Phase III data, on the expected change from baseline to Week 12 in the number of monthly migraine days and should provide adequate power for detection of a clinically meaningful treatment effect.

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

4 Ethics

4.1 Ethical Rationale

This study will evaluate eptinezumab as a potential therapeutic candidate for a target patient population who failed prior preventive treatment for CM and EM.

Inclusion of a placebo group is justified since the group is representative of the BSC allowing acute treatment of migraine when prior preventive treatments have not worked. Thus, no patient will be denied access to standard treatments.

The randomization ratio of 1:1:1 increases the possibility that the patient will receive an active treatment and ensures that the majority of patients will receive eptinezumab in the

Placebo-controlled Period. Furthermore, all patients will receive eptinezumab in the Extension Period. Thus, no patient will be denied access to active treatment with eptinezumab.

Two dose groups (100 mg or 300 mg) are considered for the current study as these have shown to be efficacious and to generally be well tolerated in the treatment of episodic and chronic migraine in the Phase III studies and will help guide the dose selection for this target difficult-to-treat population.

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 at doses of 100 and 300 mg from the Phase III studies, supporting that eptinezumab can be safely used in the current study in patients with difficult-to-treat migraine. However, it cannot be ruled out that the IMP could have adverse effects that have not yet been reported. Based on data from the nonclinical and clinical studies, and in combination with the cautionary measures implemented in the study design, the risks for the patients are considered well controlled and balanced with the potential benefits of the treatment.

In accordance with *Good Clinical Practice*,[38] qualified medical personnel at Lundbeck or the Clinical CRO will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Safety Committee to ensure that prompt action is taken, if needed.

In accordance with *Good Clinical Practice*,[38] the investigator will be responsible for all study-related medical decisions.

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.

Changing (for example, discontinuing or down-tapering) a patient's concomitant medications prior to the Screening Visit to ensure that the patient meets the selection criteria is a study-related activity and must not occur before the *Informed Consent Form* has been signed.

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 is 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.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

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

The patients must be informed:

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

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

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

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients. Prior to allowing a patient to participate in the study, an *Informed Consent Form* 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*.

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 ethics committees.

As the blood sampling for the exploratory genomic, proteomic, and metabolomic analyses is an integral part of this study, the main *Informed Consent Form* covers these analyses.

Conversely, the blood sampling for potential future genetic biomarker analysis is optional and a separate *Informed Consent Form* covers this analysis. The Exit Interview is optional, and a separate *Informed Consent Form* covers this interview.

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

A patient may, at any time and without stating a reason, specifically request the destruction of the patient's biobank 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 biobank 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[41] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck or delegate and the external organization to ensure compliance with the above-mentioned legislation.

4.4 Ethics Committees (ECs) and Institutional Review Boards (IRBs)

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 Planned Countries and Regions

Planned countries and regions: Europe and North America

Planned number of screened patients (approximately): 1680

Planned number of randomized patients: 840

5.2 Patient Recruitment

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

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

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 are eligible to participate in this study.

Inclusion Criteria

1. The patient is able to read and understand the *Informed Consent Form.*
2. The patient has signed the *Informed Consent Form*.
3. The patient, if part of the *Exit Interview subset* has provided a signed subset-specific Informed Consent Form.
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 migraine as defined by IHS ICHD-3 guidelines[1] (see section 9.1.2) with a history of chronic or episodic migraines of at least 12 months prior to the Screening Visit.
7. The patient has a migraine onset of ≤50 years of age.
8. The patient has ≥4 migraine days per month for each month within the past 3 months prior to the Screening Visit. (A migraine day is defined in section 9.1.2).
9. The patient has demonstrated compliance with the Headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit (see section 9.1.3 for *Definition of a Compliant Day*).
10. The patient fulfils the following criteria for CM or EM in prospectively collected information in the eDiary during the Screening Period (see section 9.1.3 for *Definition of a Migraine Day* and *Headache Day*):

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

11. (a) The patient has documented evidence of treatment failure* (must be supported by medical record or by physician's confirmation specific to each treatment – see chapter 12) in the past 10 years of 2-4 different migraine preventive medications out of the following:
    - propranolol/metoprolol
    - topiramate
    - amitriptyline
    - flunarizine
    - candesartan
    - valproate/divalproex
    - botulinum toxin A/B (if documented that botulinum toxin was taken for chronic migraine)

    AND

    (b) The patient has failed two of the below of which at least one must be due to inadequate efficacy:
    - propranolol/metoprolol
    - topiramate
    - amitriptyline
    - flunarizine
    - candesartan
12. The patient has a history of either previous or active use of triptans for migraine.
13. The patient is aged ≥18 and ≤75 years at the Screening Visit.
14. 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 following contraceptive methods:

* Treatment failure could have been due to inadequate efficacy (that is, no clinically meaningful improvement at the locally recommended dose for at least 3 months) and/or safety/tolerability reasons (that is, discontinuation due to adverse events) and/or contraindications (that is, ineligibility due to medical reasons). Treatment failure corresponds to the first documented failure for each medication.

- combined oral, intravaginal or transdermal hormonal contraception
- progestogen-only oral, injectable or implantable hormonal contraception
- intrauterine devices (IUD)
- intrauterine hormone-releasing system (IUS)
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide
- vasectomized partner

The contraception must be used from the Screening Visit to ≥6 months after the last dose of IMP (if hormonal contraceptives are used, see Appendix II for stability requirement for hormonal contraceptives 12 weeks prior to the Screening Visit)

15. The patient agrees to have regular contact with another adult throughout the study (if applicable for sites in the Czech Republic).

Exclusion Criteria

1. The patient has previously been enrolled in this study.
2. The patient has experienced failure on a previous treatment targeting the CGRP pathway.
3. The patient has a treatment failure on valproate/divalproex or botulinum toxin A/B and the treatment is not the latest preventive medication prior to study inclusion. The medication is regarded as the latest if the medication start date is after the start date of the other preventive medications and the medication stop date is after the stop date of the other preventive medications.
4. The patient has participated in a clinical study <30 days or has taken any investigational drug within 5 plasma half-lives (whichever is longer) prior to the Screening Visit.
5. 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.
6. The patient is pregnant or planning to become pregnant or breastfeeding.
7. The patient has a history of severe drug allergy or hypersensitivity or known hypersensitivity or intolerance to the IMP or its excipients.
8. The patient has confounding and clinically significant pain syndromes, (for example, fibromyalgia, chronic low back pain, complex regional pain syndrome).
9. The patient has a diagnosis of acute or active temporomandibular disorder.
10. The patient has a history or diagnosis of chronic tension-type headache, hypnic headache, cluster headache, hemicrania continua, new daily persistent headache, unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), ophthalmoplegic migraine, or migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
11. The patient has any current psychiatric condition that is uncontrolled and/or untreated for a minimum of 6 months prior to the Screening Visit. Patients with a lifetime history of psychosis and/or mania in the last 5 years prior to the Screening Visit are excluded.
12. The patient has a current diagnosis or history of substance abuse or alcohol abuse (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 migraine 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 IMP.
16. The patient has a history of clinically significant cardiovascular disease or 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 Body Mass Index (BMI) $\geq$39 kg/m^2 at the Screening Visit.
21. The patient has tested positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (anti-HCV) at the Screening Visit.
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
    - a PR interval >200 ms
    - a QRS interval >130 ms
    - a QT_{cF} interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where $QT_{cF} = QT/RR^{0.33}$) OR a QT_{cF} interval >440 ms (for men) or >460 ms (for women) if the patient has a heart rate <60 bpm.
24. The patient is, at the Screening Visit or Baseline Visit, at significant risk of suicide (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 12 months).

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.

5.4 Withdrawal Criteria

A patient must be *withdrawn from the study* if:

- the patient withdraws consent (defined as a patient who **explicitly** takes back their consent); section 8.9 states how the patient's data will be handled
- the patient has been randomized in error and has not received IMP
- 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 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
- any site personnel break the randomization code for that patient
- the patient becomes pregnant
- the patient experiences an anaphylactic reaction or another severe and/or serious hypersensitivity reaction to the IMP infusion, as assessed by the investigator. If the event occurs during the IMP infusion, the infusion must be discontinued immediately
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing <2 weeks later
- the patient has a QT_{cF} interval >500 ms; the decision to withdraw the patient may be postponed until a repeat ECG is taken, if it is taken within 24 hours
- the patient 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)

Patients who withdraw will not be replaced.

6 Investigational Medicinal Product(s) (IMP(s))

6.1 Treatment Regimen

Patients will be randomly allocated via a centralized randomization system to one of three treatment groups: eptinezumab 300 mg, eptinezumab 100 mg, or placebo, in a ratio of 1:1:1.

The patient will receive IMP starting from the Baseline Visit to follow a Q12W dosing schedule with either eptinezumab or placebo by IV infusion.

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

6.2 IMP(s), Formulation(s), and Strength(s)

The IMP(s) supplied by Lundbeck in this study are:

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

Patients allocated to the 300 mg eptinezumab treatment group will be dispensed 3 x 100 mg, Solution for Infusion 100 mg/ml added to 100 mL of 0.9% normal saline, intravenously.

Patients allocated to the 100 mg eptinezumab treatment group will be dispensed 1 x 100 mg, Solution for Infusion 100 mg/ml added to 100 mL of 0.9% normal saline, intravenously.

Patients allocated to the placebo treatment group will be dispensed 100 mL of 0.9% normal saline, intravenously.

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

Doses will be administered intravenously over a period of 30 (+15) minutes by the blinded investigator or designee.

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

6.3 Manufacturing, Packaging, Labelling, and Storage of IMPs

The IMP(s) 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 single-use vials (as a concentration 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 IMPs will be identified using a unique IMP number.

The IMPs must be stored in a safe and secure location, and in accordance with the storage conditions specified on the labels. Please refer to the *Pharmacy Manual* for additional storage and handling procedures.

6.4 Method of Assigning Patients to Treatment

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

6.5 IMP Accountability

IMP accountability will be documented in the IRT by the unblinded CRA.

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

6.6 Unblinding Procedures

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

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

The investigator may only break the code for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator must consult the CRA in some cases it may be the medical monitor before breaking the code. The investigator must record the date and reason for breaking the code on the *IMP Code Break Form*. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Form*. The CRA (in some cases it may be the medical monitor) must be notified immediately. The IRT will capture the date and time of the code break call. Information on the allocated treatment will be provided during the call and by fax or email, depending on availability/preference. When the code is broken for a patient, the patient must be immediately withdrawn from the study. If this occurs during a visit, the investigator must

complete the visit as a Withdrawal Visit; otherwise, the patient will be asked to attend a Withdrawal Visit 12 weeks after his/her last dose of IMP.

6.7 Post-study Access to IMP(s)

Patients in the study will have access to appropriate medical care after they complete or withdraw from the study.

7 Concomitant Medication

7.1 General

Concomitant medication is any medication other than the IMP that is taken during the study up until the Completion/Withdrawal Visit, including during the Screening Period.

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

Details of all migraine preventive treatment failures (prescription and over-the-counter) taken ≤10 years prior to the Screening Visit must be recorded in the eCRF at the Screening Visit.

For any concomitant medication for which the dose has been 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.

7.2 Use of Coronavirus Disease 2019 Vaccine

There are currently no data indicating that eptinezumab interacts with or impairs 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 described in Appendix II. All adverse events, including those judged by the investigator to be related to the COVID-19 vaccine, must be recorded in the eCRF (see section 10.1.1). A causality assessment, including an alternative causality as relevant, must be provided.

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 chapter 9.

The Screening Visit (Visit 1) is performed 28 to 30 days before the Baseline Visit (Visit 2).

Thereafter, study visits are divided into Phone Contacts and IMP Visits. The Primary Outcome Visit (Visit 5) is performed 12 weeks after the Baseline Visit. Patients will continue until the Completion Visit (Visit 20) or until the Withdrawal Visit.

At Visit 8 patients will enter the Extension Period and receive either one of two treatments: eptinezumab 300 mg or eptinezumab 100 mg until the Completion Visit (Visit 20).

Patients will complete a daily headache eDiary from the time of screening until the Completion/Withdrawal Visit. Patients will be given a headache eDiary at the Screening Visit and must be trained in its use and compliance requirements. Patients will complete electronic headache diary entries daily. At each clinic visit and phone contact (that is every 4 weeks), a compliance check of the eDiary will be conducted. Patients must continue to complete the daily eDiary during the transfer to the Extension Period. Headache data from the eDiary will be made available during the study to site staff for review via the eDiary system portal. See section 9.2.2 for further details on eDiary.

All assessments may be completed over a maximum of 2 consecutive days (with the exception of PROs - see below); if so, the first day is considered the "visit" day according to the schedule. 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.

PROs which are scheduled in alignment with a clinic visit can be completed in the clinic or in the remote setting within 3 days prior to the scheduled clinic visit date. PROs which are scheduled in alignment with a phone contact (PGIC (at Week 4 only), HIT-6, EQ-5D-5L, HCRU, WPAI) 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 prior to the Screening Visit.

In some cases patients may be asked to attend up to 2 Screening Visits to complete all assessments at screening. In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended with approval from the sponsor provided the Lundbeck medical expert accepts the rationale provided for the extension.

At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary and with training of efficacy and pharmacoeconomic assessments (PROs). Details will be provided in a separate user manual. See section 9.2.2 for further details on eDiary.

Exit Interview subset: at the Screening Visit, the patients undergoing the Visit 8 exit interviews must provide a signed subset-specific Informed Consent. Details will be provided in a separate exit interview guide. See section 9.5.1 for further details on exit interview.

8.2.1 Pre-screening

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

Prior to the Baseline Visit, a study-specific *Eligibility Form* must be completed by the site and transmitted to the CRO for their review. A confirmation that the patient can continue further with the study procedures is required before randomization.

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

Rescreening is only allowed for patients with a *complete* Screening Visit and who do not fulfil:

- 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.

Rescreening may also be allowed for patients with a *complete* Screening Visit but are required to be in quarantine due to a positive COVID-19 test.

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.

Authorization for re-screening may only be granted by the sponsor's medical expert (or the CRO's medical monitor) after a thorough review of all data from the original Screening Visit.

At the new Screening Visit, the patient must sign a new *Informed Consent Form*. 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 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 authorized by the sponsor's medical expert (or 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.

8.3 Baseline Visit + IMP (Visit 2)

In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended with approval from the sponsor provided the Lundbeck medical expert accepts the rationale provided for the extension.

The Baseline Visit also includes IMP administration and will occur 28-30 days after the Screening Visit. Inclusion and exclusion criteria review must be done prior to dosing at the Baseline Visit.

For procedures preceding and following IMP administration, see section 8.5.

8.4 Primary Outcome + IMP (Visit 5)

The Primary Outcome Visit comprises assessments of the primary, secondary and exploratory endpoints. The Primary Outcome Visit also includes IMP administration. For procedures preceding and following IMP administration, see section 8.5.

8.5 IMP Visits (Visits 2, 5, 8, 11, 14, 17)

At the IMP Visits, the infusion is preceded by assessments of vital signs including body temperature, concomitant medications, AEs, physical examination, ECG, blood and urine sampling and C-SSRS administration.

Assessments involving interviews and scales must be administered before the infusion. PROs will be completed in the clinic the following order; HIT-6, PGIC, MBS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI. Alternatively, PROs which are scheduled in alignment with an IMP visit can be completed in the remote setting within 3 days prior to the scheduled clinic visit date.

Patients must complete the daily eDiary entries prior to infusion. A compliance check of the eDiary will be conducted and the patient must be assisted with re-training if necessary. See section 9.2.2 for further details on eDiary.

Patients will be monitored for at least 1 hour following end-of-infusion and before being discharged from the clinic. Patients will be requested to stay longer should the investigator 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. Vital signs including body temperature, infusion related reactions (IRRs) and AEs will be checked after infusion and before the patient is discharged from the site. AEs should be collected prior to assessment of IRRs.

Exit Interview subset: The exit interview will be conducted at Visit 8 (Week 24 Visit or at the Withdrawal Visit for patients who withdraw prior to Week 24). The exit interview must be conducted after all visit assessments are completed. A visit window of 2 weeks is allowed for the exit interview from the last assessment conducted for Visit 8/Withdrawal Visit (for patients who withdraw prior to Week 24). See section 9.5.1 for further details on the exit interview.

8.6 Phone Contacts (Visits 3, 4, 6, 7, 9, 10, 12, 13, 15, 16, 18, 19)

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

A compliance check of the eDiary will be conducted and the patient must be assisted with re-training if necessary. See section 9.2.2 for further details on eDiary.

Additionally, the following PROs must be completed in the remote setting in alignment with the scheduled phone contacts (see Panel 2): PGIC (at Week 4 only), HIT-6, EQ-5D-5L, HCRU, WPAI. These can be completed on the day or within 3 days prior to the scheduled phone contact date.

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

Phone contacts should be planned to maintain the visit schedule relative to the Baseline Visit.

8.7 Completion Visit (Visit 20)

Patients who complete the study will attend a Completion Visit. As the visit will be scheduled 12 weeks after the last dose of IMP, the Completion Visit will also serve as a Safety Follow-up Visit for all patients (section 8.10).

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

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

8.8 Unscheduled Visit

An unscheduled visit may occur throughout this study if needed. Unscheduled visits can be completed if required as either site or telephone visits. At these visits clinical safety laboratory tests, ECG, vital signs 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 chapter 10) or documented in the medical notes as applicable.

8.9 Withdrawal Visit

Patients who withdraw from the study will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled 12 for weeks after the last dose of IMP after withdrawal.

As the Withdrawal Visit will be scheduled 12 weeks after the last dose of IMP, this visit will also serve as a Safety Follow-up Visit for all withdrawn patients (section 8.10). Patients who withdraw prior to Week 24 will undergo additional efficacy evaluations, thus for these patients the Withdrawal Visit will also serve as an Efficacy Follow-up Visit.

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

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

The reason for withdrawal must be recorded in the eCRF.

For a patient who withdraws consent:

- if the patient withdraws consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including that visit will be used
- if the patient withdraws consent during a telephone conversation, the investigator will ask the patient if they will attend a Withdrawal Visit 12 weeks after their last dose. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including that visit will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical records
- if the patient explicitly requests that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected

8.10 Safety Follow-up at Completion or Withdrawal Visit

As the Completion or Withdrawal Visit will be scheduled 12 weeks after the last dose of IMP, these visits will also serve as Safety Follow-up Visits.

A safety follow-up is conducted to capture adverse events that occur after the last IMP or Phone Contact Visit (whichever is later) as well as to follow up on the outcome of adverse events ongoing at that visit at the Completion/Withdrawal Visit.

For adverse events that were ongoing at the last IMP or Phone Contact Visit and that resolved by the Completion/Withdrawal Visit, the stop date must be recorded. For non-serious adverse events still ongoing at the Completion/Withdrawal Visits, the *Ongoing Adverse Event* checkbox on the *Adverse Event Form* must be ticked. SAEs must be followed until resolution or the outcome is known.

For patients with a clinically significant out-of-range clinical safety laboratory test value at the Completion or Withdrawal Visit or who withdrew due to an elevated AST or ALT value (see section 5.4), safety follow-up should be scheduled and recorded in the patients' medical records and not in the eCRF; see section 10.5 for details.

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

8.11 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.

The following assessments will be performed after the *Informed Consent Form* has been signed:

- Demographics (age, sex, race)
- Prior migraine treatment history for review and documentation of previous treatment failure of different migraine preventive medications (see below for definition of previous treatment failure and chapter 12 for required documentation)
- Other recent medication

- Disease-specific history
- Relevant history (medical, psychiatric, neurological)
- Physical examination
- Substance use
- Height and weight without shoes
- Signs and symptoms present at screening and/or baseline (before IMP intake)
- Vital signs, ECGs
- C-SSRS
- Blood and urine samples for screening (for example., β-HCG, FSH, HIV, HBsAg, anti-HCV) and other clinical safety laboratory tests (as listed in Panel 5)

Definition of previous treatment failure of different migraine preventive medications.

- (a) The patient has documented evidence of treatment failure* in the past 10 years of 2-4 different migraine preventive medications out of the following:
  - propranolol/metoprolol
  - topiramate
  - amitriptyline
  - flunarizine
  - candesartan
  - valproate/divalproex
  - botulinum toxin A/B (if documented that botulinum toxin was taken for chronic migraine)

  AND
- (b) The patient has failed two of the below of which at least one must be due to inadequate efficacy:
  - propranolol/metoprolol
  - topiramate
  - amitriptyline
  - flunarizine
  - candesartan

See chapter 12 for acceptable documented evidence of previous treatment failures.

* Treatment failure could have been due to inadequate efficacy (that is, no clinically meaningful improvement at the locally recommended dose for at least 3 months) and/or safety/tolerability reasons (that is, discontinuation due to adverse events) and/or contraindications (that is, ineligibility due to medical reasons). Treatment failure corresponds to the first documented failure for each medication.

9.1.2 Diagnostic Assessments

IHS ICHD-3 guidelines[1] sections 1.1, 1.2 and 1.3 for Migraine or Chronic Migraine are the diagnostic criteria to be used when assessing patient eligibility.

Panel 4 IHS ICHD-3 guidelines[1] for Migraine

1.1 Migraine without aura	1.2 Migraine with aura
A. At least five attacks fulfilling criteria B–D B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (for example, walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis.	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5–60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.
1.3 Chronic migraine	
A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura C. On ≥8 days/month for >3 months, fulfilling any of the following: 1. criteria C and D for 1.1 Migraine without aura 2. criteria B and C for 1.2 Migraine with aura 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis.	

9.1.3 Classifications for Eligibility

Fulfilment of criteria for EM or CM according to the inclusion criteria in this protocol will be confirmed via prospectively collected information in the eDiary during the screening period.

Definition of a Migraine Day: A *migraine day* is defined as a day with a headache that:

- lasts ≥4 hours and meets ICHD-3 criteria C and D for migraine without aura (1.1), OR
- lasts ≥30 minutes and < 4 hours AND the patient took medication because he/she believed that he/she had a migraine AND meets ICHD-3 criteria C and D for migraine without aura (1.1)

The characteristics of each headache, will be collected in the eDiary at the end of the headache, and for each headache it will be determined whether it qualifies as a migraine. If a headache qualifies as migraine, every day the headache lasted will count as a *migraine day*.

Headaches that were ongoing on the last day of the Screening Period will be classified as migraines for the eligibility calculation.

Definition of a Headache Day: A *headache day* is defined as a day with a headache that lasts ≥30 minutes or that meets the definition of a *migraine day*.

Definition of an eDiary Compliant Day: A *compliant day* is defined as any day where an evening diary is completed OR a headache diary is completed

9.1.4 Definitions for Baseline Disease Activity and Analysis

The following definitions will be applied for calculation of number of EM/CM patients (and low/high frequency EM patients) for subgroup analyses:

Definition of a Migraine Day: The definition is based on the IHS guidelines[42] for controlled studies of preventive treatment of CM in adults. A *migraine day* is defined as a day with a headache that:

- lasts ≥4 hours and meets ICHD-3 criteria C and D for migraine without aura (1.1),
- or lasts ≥30 minutes and where the patient had an aura with the headache (migraine with aura*)
- or lasts ≥30 minutes and meets two of the three ICHD-3 criteria B, C and D for migraine without aura (1.1) (probable migraine**),
- or is a day where the patient took migraine medication because he/she believed that he/she had a migraine***

The characteristics of each headache, will be collected in the eDiary at the end of the headache, and for each headache it will be determined whether it qualifies as a migraine. If a headache qualifies as migraine, every day the headache lasted will count as a *migraine day*.

If a headache lasts ≥72 hours, the days will be counted as *headache days* or *migraine days* as aligned with the IHS guidelines.[42]

Further details on the definitions:

*) At the Screening Visit, the patient's usual aura is described. The patient will be asked about occurrence of aura based on questions in the eDiary as follows: *"Have you experienced aura with this headache?"*

**) For probable migraine, the definition in the protocol is based on ICHD-3 criteria for probable migraine (1.5) with the exception of criterion A in 1.1 *Migraine without aura* (At least five attacks fulfilling criteria B-D) . For criterion B in 1.1 *Migraine without aura* if a headache lasts more than 72 hours, the days will still be counted as *headache/migraine days* as aligned with the IHS guidelines.[42] The definition does not include *probable migraine with aura,* as detailed aura criteria are not collected in the eDiary and hence it is not possible to check if one criterion is missing.

***) If patients are taking acute migraine medication, the following questions are captured in the eDiary: "*Did you take any medications to treat this headache?"* and "*Did you take this medication because you believed that you were having a migraine?"* Only if both are affirmed, will the headache be classified as a migraine.

Definition of a Headache Day: A *headache day* is defined as a day with a headache that lasts ≥30 minutes or that meets the definition of a *migraine day*.

Definition of a Migraine Attack: A migraine that meets the definition of a migraine is also referred to as a *migraine attack*.

Definition of a Headache Episode: A headache that either lasts ≥30 minutes or meets the definition of a migraine, is also referred to as a *headache episode.*

9.2 Efficacy Assessments

The eDiary assessments will be completed by the patient in the remote setting on a daily basis. At each clinic visit and phone contact (that is every 4 weeks), a compliance check of the eDiary will be conducted. On clinic visit days, patients must complete the daily eDiary entries prior to infusion.

On clinic visit days, efficacy assessments include PROs (PGIC and MBS) and will be completed in the clinic along with the pharmacoeconomic PROs (see section 9.3). The PROs must be completed before the infusion and in the following order; HIT-6, PGIC, MBS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI. Alternatively, PROs that are scheduled in alignment with a clinic visit can be completed in the remote setting within 3 days prior to the scheduled clinic visit date.

PGIC which is scheduled in alignment with a phone contact (at Week 4) 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 Use of COA Tools

The COA tools are PROs, and guidance will be given to the patients on how to complete them.

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:

- eDiary – to assess daily headache and migraine variables, that is the number of hours with headache, presence of associated symptoms, and use of acute migraine medications start and stop dates, headache severity
- PGIC - to assess overall change in the severity of illness following treatment
- MBS - to assess a migraine-related symptom that is most bothersome for the patient

Detailed instructions on how to complete/administer the COA tools will be provided to the site in a *PRO Guideline*.

9.2.2 eDiary

The patient will be instructed to complete an electronic diary (eDiary) daily from the Screening Visit until the Completion/Withdrawal Visit. The eDiary consists of applications and reports which will be used to derive the migraine and headache endpoints. At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary. During the Completion/Withdrawal Visit, eDiary close out must be performed while the patient is on site. Details will be provided in a separate user manual.

At the Screening Visit, each patient will receive comprehensive training from site staff on the use of the eDiary. Site staff will also instruct patients on the requirement for timely and daily completion of the eDiary. The content of the headache diary is developed on key symptoms and characteristics as mentioned in the definition of migraine (see section 9.1.2). The day of eDiary distribution will start the 28-day eDiary Screening Period during which the patient will record daily information regarding headache characteristics, severity, length, and intake of headache/migraine medication. Headache and migraine items will be assessed with a yes/no response; and severity will be rated as mild, moderate or severe. An eDiary Eligibility Report will be used to summarize baseline headache and migraine days and eDiary compliance during the Screening Period. Any patient found to be ineligible for the study during the screening period or prior to randomization or dosing will not be randomized or dosed.

On each day during the study until the Completion/Withdrawal Visit, the patient will be asked to record diary data for the previous 24-hour period. For each day, the patient should record if they experienced any headache. For each experienced headache, the start and stop date and time will be collected. Information included in the definition of a migraine (for instance, headache severity, additional symptoms, and use of acute medication) will also be collected. Additional details regarding the questions that patients will answer can be found in the *eDiary*

User Manual. Headache and Compliance data from the eDiary will be made available during the study to site staff for review via the eDiary system portal. At least 85% compliance is needed during the screening period and throughout the study until the Completion/Withdrawal Visit. Site staff will counsel patients as needed on the importance of completing the eDiary daily. All follow-up with patients regarding eDiary compliance should be documented in the source records.

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

9.2.3 Patient Global Impression of Change (PGIC)

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

9.2.4 Most Bothersome Symptom (MBS)

The Investigator will verbally obtain the most bothersome symptom associated with the patient's migraines during the Baseline Visit. Patients will be asked to rate the improvement in this symptom from baseline on a 7-point scale identical to the scale used for the PGIC. The MBS areas include: nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, other. It takes less than 5 minutes to complete the MBS.

9.2.5 External COA Monitoring Oversight

Lundbeck reserves the right to use external quality oversight methods to ensure eDiary compliance and PRO data quality, as well as ensure accurate administration of the COAs. For this study, the CRO will conduct the external data monitoring (to be agreed with the sponsor) which will include the following quality oversight methods:

- Compliance check
- Independent review of source documents
- Clinical data analytics review

9.2.6 COA Tool Training

COA training will be conducted by the CRO (as agreed with the sponsor). Site staff will complete their designated training curriculum based on their initial qualification status and assigned role. The training program will also include general COA quality assurance and management guidance.

The patients will be trained on how to use the PROs by site staff who have adequate experience with migraine and have received adequate training on good standards in providing guidance to patients on how to use the PROs. Any exceptions must be discussed and approved by Lundbeck and/or its designee.

Only site staff who have received adequate training on good standards in administering the HIT-6, PGIC, MBS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI will be authorized to train the patients on completion of PROs in the study. Documentation of training will be provided to site staff for archiving in the investigator trial master file (TMF). New PRO trainers joining the study must be trained similarly.

COA training will be conducted by the CRO.

9.3 Pharmacoeconomic Assessments

On clinic visit days, pharmacoeconomic assessments include PROs (HIT-6, MSQ v2.1, EQ-5D-5L, HCRU, WPAI) and will be completed in the clinic along with the efficacy PROs (see section 9.2). The PROs must be completed before the infusion and in the following order; HIT-6, PGIC, MBS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI. Alternatively, PROs that are scheduled in alignment with a clinic visit can be completed in the remote setting within 3 days prior to the scheduled clinic visit date.

Additionally, HIT-6, EQ-5D-5L, HCRU, WPAI which are scheduled in alignment with phone contacts 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 (see Panel 2).

9.3.1 Clinical Outcome Assessments (COAs)

9.3.1.1 Use of COA Tools

Refer to section 9.2.1 for further information on use of COA tools.

The following COA tools will be used:

- HIT-6 - to assess the impact of an occurring headache and its effect on the ability to function normally in daily life
- MSQ v2.1 - to assess quality of life related to migraine
- EQ-5D-5L - to assess the overall state of health
- HCRU - to assess migraine-specific healthcare resource utilization
- WPAI - to assess overall effect of health on productivity at work and daily activities

9.3.1.2 Headache Impact Test (HIT-6)

The HIT-6 (v1.0)[43] is a Likert-type, self-reporting questionnaire designed to assess the impact of an occurring headache and its effect on the ability to function normally in daily life. The HIT-6 contains 6 questions, each item is rated from “never” to “always” with the following

response scores: never = 6, rarely = 8, sometimes = 10, very often = 11, and always = 13. The total score for the HIT-6 is the sum of each response score and ranges from 36 to 78. The life impact derived from the total score is described as followed: Severe (≥60), Substantial (56-59), Some (50-55), Little to None (≤49). It takes less than 5 minutes to complete the HIT-6 questionnaire.

9.3.1.3 Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQ v2.1)

The MSQ v2.1[44] is a patient-reported outcome designed to assess the quality of life in patients with migraine. It consists of 14 items covering three domains: role function restrictive (7 items); role function preventive (4 items); and emotional function (3 items). Each item is scored on a 6-point scale ranging from 1 (none of the time) to 6 (all of the time). Raw domain scores are summed and transformed to a 0 to 100 point scale. Higher scores indicate better quality of life. It takes approximately 5-10 minutes to complete the MSQ v2.1.

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

The EQ-5D-5L[45] is a patient-reported assessment designed to measure the patient's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS ranges from 0 (*worst imaginable health state*) to 100 (*best imaginable health state*). It takes approximately 5 minutes to complete the EQ-5D-5L.

9.3.1.5 Health Care Resource Utilization (HCRU)

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

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

The WPAI[46] is a patient self-rated scale designed to provide a quantitative measure of the work productivity and activity impairment due to a specific health problem (WPAI:M). The WPAI assesses activities over the preceding 7 days and consists of 6 items: 4 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.

9.3.1.7 External COA Monitoring Oversight

See section 9.2.5

9.3.1.8 COA Training

See section 9.2.6

9.4 Safety Assessments

9.4.1 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. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of each adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See chapter 10 for further information on adverse events.

9.4.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 5.

Panel 5 Clinical Safety Laboratory Tests

Haematology	**Liver**[b]	**Serology**[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-HIV [HIVAB] S-HBsAg [HBSAG] S-anti HCV [HCAG]
		Infection[c] S-C-reactive protein [CRP]
Electrolytes[b]	**Kidney**[b]	**Urine**[d]
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]
Endocrine and Metabolic[b]	**Lipids**[b,e]	**Pregnancy**[f]
S-albumin [ALB] B-glucose[e] [GLUC] B-HbA_{1c} [HBA1C] P-creatine phosphokinase [CK] S-thyroid-stimulating hormone[c] [TSH] S-follicle-stimulating hormone[g] [FSH]	S-low density lipoprotein [LDL] S-high density lipoprotein [HDL] S-triglycerides [TRIG] S-cholesterol (total) [CHOL]	S-human chorionic gonado-tropin [HCG] Urine (dipstick)
B = blood; P = plasma; S = serum; U = urine; [ ] = CDISC term		

a Count and % of total leucocytes.

b Clinical chemistry.

c Performed at the Screening Visit only. In case of abnormal TSH, reflex testing of T3 and T4 will be conducted. In case of positive or indeterminate results for serology, confirmatory testing will be performed including viral load.

d In case of a positive urine dipstick, a microscopic evaluation will be done.

e Fasting, when possible.

f Only for women of childbearing potential. Pregnancy test at the Screening Visit to be performed using serum β-HCG. At all other visits, urine pregnancy testing will be performed and in case of a positive finding, confirmatory testing will be performed via serum β-HCG.

g Only for women at the Screening Visit.

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed at the central laboratory.

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

documented on the laboratory report, until the value has stabilized or until the value has returned to a clinically acceptable value (regardless of relationship to the IMP). A patient with a value that is out-of-range at the Completion or Withdrawal Visit and considered clinically significant must be followed in accordance with usual clinical practice until the value normalizes or stabilizes or a diagnosis or reasonable explanation has been established. Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical records.

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

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

9.4.3 Vital Signs

The investigator may appoint a designee (for example, nurse or paramedic) to measure vital signs including body temperature, provided this is permitted according to local regulations and provided the investigator has trained the designee how to measure these. 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. Pulse rate will be recorded before each blood pressure measurement.

Vital signs including body temperature must be assessed prior to blood sampling.

Any out-of-range values considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.4.4 Height and Weight

The patient's height will be measured.

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

Any weight change considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.4.5 Electrocardiograms (ECGs)

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

The investigator will be provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory.

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

The investigator has the final decision on the interpretation of the ECG results. Any abnormal ECG result or out-of-range ECG parameter value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.4.6 Physical Examination

The investigator may appoint a designee to be primarily responsible for performing the physical examinations, provided this is permitted according to local regulations. The investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all the physical examinations.

The physical examination must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen, genito-urinary system, and musculoskeletal system and must be performed by a physician or physician assistant.

Any abnormal finding or out-of-range value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.4.7 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.[47] 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 1year assessment) and the “Since last visit” version (for all subsequent visits). It takes approximately 5 minutes to administer and rate the C-SSRS.

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

The C-SSRS should only be administered by a rater who has adequate experience with clinical studies in CNS indications. The rater should be a clinician, such as a neurologist, geriatrician, psychiatrist, or (neuro-) psychologist involved in clinical practice or regularly evaluating patients. Any exceptions must be discussed and approved by Lundbeck and/or its designee. 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.

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

9.4.8 Anti-Drug Antibody (ADA) including Neutralizing Antibody (NAb) Assessments

Blood samples for the ADA including NAb assessments will be collected as outlined in Panel 2.

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

Blood samples (2 mL per occasion) for ADA including NAb analysis will be collected in silica clot activator tubes. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed by Charles River under the responsibility of Department of Bioanalysis, H. Lundbeck A/S, according to a protocol approved by Lundbeck before the serum samples are analysed.

9.5 Other Assessments

9.5.1 Exit Interview (subset)

At the Week 24 Visit/Withdrawal Visit (for patients who withdraw prior to Week 24), the site personnel should remind patients of the exit interview, which is to be conducted shortly after the last assessment of the Week 24 Visit and no later than 2 weeks after the Week 24 Visit/Withdrawal Visit (for patients who withdraw prior to Week 24). The interviews will be conducted by an external designated qualitative study interviewer. The investigator will schedule the patient exit interview at the patient's convenience. The patient exit interview will take up to 60 minutes in total and collect qualitative information on the patient's experiences with migraine related to disease impact on daily activities, social and professional life. Exit interviews will help better understand experiences with disease, gain additional insight into trial data, support interpretation of quantitative assessments and endpoints to discuss meaningfulness of change. Additional aspects identified by a focused literature review and pilot exit interviews, may also be discussed to collect the patient´s treatment experience. Details will be provided in separate *Exit Interview Guidelines*.

The data will not be included in the CSR. The coding, analysis and reporting of exit interview data will be performed by the CRO based on a separate analysis plan.

9.6 Biobanking

9.6.1 General Considerations

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

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

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

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

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

9.6.2 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 25 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 CRO or by a bona fide research collaborator.

9.6.3 Blood Sampling for Metabolomics and/or Proteomics

Blood samples for plasma separation and metabolomics and/or proteomics will be collected in one 10 mL K_2 EDTA tube in accordance with Panel 2. The maximum volume of blood to be collected during the study for this purpose will be 50 mL.

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

9.6.4 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 K_3 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 CRO or by a *bona fide* research collaborator.

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

9.6.5 Blood sampling for possible future anti-drug antibody assessments

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

The maximum volume of blood to be collected during the study for this purpose will be 4 mL.

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

9.7 Order of Assessments

The assessments should preferably be administered in the following order:

- No study related activities must be conducted until after the applicable *Informed Consent Form* is signed.
- Screening Visit:
  - Blood and urine sampling for clinical safety laboratory tests must be scheduled and results reviewed prior to the Baseline Visit.

  - At the Screening Visit the "Baseline/Screening" version of the Columbia-Suicide Severity Rating Scale will be used. At each following visit, the "Since Last Visit" version of the C-SSRS will be used.
- Clinic Visits:
  - PROs must be completed at the patient's convenience before or after blood and urine sampling.
  - On clinic visit days, patients must complete the daily eDiary entries prior to infusion.
  - PROs completed in the clinic must be done before the infusion. HIT-6 should preferably be the first PRO completed, followed by the PGIC, MBS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI. Alternatively, PROs that are scheduled in alignment with a clinic visit can be completed in the remote setting within 3 days prior to the scheduled clinic visit date. It is also preferable that the same order of assessments is used per patient and if the scheduled time of the day for the assessments is as consistent as possible across all the study visits.
  - Infusion must be preceded by the assessment of vital signs including body temperature, concomitant medications, AEs, physical examination, ECG, blood sampling and urine sampling and C-SSRS administration. Vital signs must be assessed prior to blood sampling.
  - Vital signs including body temperature, IRRs and AEs will be checked after infusion and before the patient is discharged from the site. IRRs must be assessed after the AE collection. For procedures preceding and following IMP administration, see section 8.5.
- Clinic Visits and Phone Contacts:
  - A compliance check of the eDiary must be conducted and the patient must be assisted with re-training if necessary. See section 9.2.2 for further details on the eDiary.
- Phone Contacts:
  - The patient will be contacted via phone every 4 weeks between infusion visits for eDiary compliance check, to ensure that selected assessments (PGIC (at Week 4 only), HIT-6, EQ-5D-5L, HCRU, WPAI) have been completed and for collection of relevant information such as AEs and concomitant medication.
- *Exit Interview subset*: The exit interview will be conducted shortly (no later than 2 weeks) after Visit 8 (Week 24 Visit or at the Withdrawal Visit for patients who withdraw prior to Week 24). The exit interview must be conducted after all visit assessments are completed. A visit window of 2 weeks is allowed for the exit interview from the last assessment conducted for Visit 8/Withdrawal Visit (for patients who withdraw prior to Week 24). See section 9.5.1 for further details on the exit interview.

9.8 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 300 mL during the study.

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

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

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

9.9 Treatment Compliance

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

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

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

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[48]

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.

It is Lundbeck policy to collect and record all adverse events, including pre-treatment adverse events, that is, those that start after the patient has signed the *Informed Consent Form* and prior to the first dose of IMP.

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

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)

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

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

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

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

Suspected unexpected serious adverse reaction (SUSAR) – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure*[29]), and related to a medicinal product by either the investigator or Lundbeck.

Overdose – is a dose taken 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 the IMP using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

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

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

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

Assessment of Outcome

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

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

10.2 Pregnancy

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

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

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

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

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

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

10.4 Reporting Serious Adverse Events (SAEs)

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

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

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

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

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*[49] and in Norway, Liechtenstein,

and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ECs.

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

10.5 Treatment and Follow-up of Adverse Events

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

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

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

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

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

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

10.6 Management of Reactions to Study Drug

There are no specific antidotes to eptinezumab. A medical emergency should be treated appropriately by the Investigator using proper standard of care and according to local guidelines for that emergency condition. Emergency equipment and medication for the treatment of these potential adverse events must be available for immediate use.

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

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

10.7 Data Monitoring Committee (DMC)

The DMC will consist of medical doctors with speciality relevant to the fields of neurology and cardiology, as well as a biostatistician. The DMC will monitor safety data on an ongoing basis in addition to cumulative safety data. The DMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC will not be involved in other study-related tasks. The DMC procedures are described in the *Data Monitoring Committee Charter*.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms (eCRFs)

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

The eCRFs use third party software (Rave®) to capture data via an online system on a computer. When the investigator enters data in the eCRF (ideally during the visit or as soon as possible [<3 days] thereafter), the data will be recorded electronically in a central database over encrypted lines, and all entries and modifications to the data will be logged in an audit trail. Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

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

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

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

11.1.2.2 Serious Adverse Event Fallback Forms

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

11.1.3 External Data

All electronic data will be transferred using a secure method accepted by Lundbeck.

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

- eDiary data
- Exit Interview results
- ECG results
- Clinical Safety Laboratory data
- Biobanking data: RNA, Metabolomics/Proteomics, ADA including NAb, DNA (optional)
- Blood ADA including NAb data

In case of any electronic Assessment(s) COA(s)/PRO(s) the results will be transferred by designated vendor.

11.2 Retention of Study Documents at the Site

11.2.1 eCRF Data

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

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

11.2.2 Other Study Documents

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

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

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

12 Monitoring Procedures

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

If the investigator does not have a patient's medical records, the investigator/designee must attempt to obtain copies or a written summary of relevant medical records from the doctor who had treated the patient earlier and include the pertinent documentation in the patient's medical records at the site. The investigator/designee must obtain general medical history prior to the study and acceptable documented evidence of previous treatment failures $\leq$10 years prior to the Screening Visit (see below).

Acceptable documented evidence of previous treatment failures.

Confirmation must be specific to each treatment failure. Treatment failure corresponds to the first documented failure for each medication:

- Medical record with medication's name, treatment duration, dose level and reasons for discontinuation, OR,
- If the investigator is also the treating physician, the investigator can provide a dated and signed written note with the above information, OR,
- If the investigator is not the treating physician, the investigator can interview the treating physician to confirm the above information and document the interview with date and name of the treating physician in the patient's medical notes, OR,
- If the investigator is not the treating physician, the investigator can request a written note from the treating physician with the above information signed and dated by the treating physician.

If none of the above can be obtained the patient is not eligible for the study.

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

Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine and verify any records that are important for the evaluation of the study. If it is not possible to perform an on-site visit, medical records may be remotely accessed by the CRA in accordance with local and national regulations.

13 Audits and Inspections

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

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

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

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

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

14 Protocol Compliance

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

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

15 Study Termination

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

- safety concerns
- proven lack of efficacy of the IMP in other studies

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

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

- For the reporting of the Placebo-controlled Period, the Classification Meeting will be held after the data base release for the reporting of the Placebo-controlled Period but before the blind has been broken and will concern the classification into APTS and FAS.

- For the addendum to the CSR, the Classification Meeting will be held after the data base release for the reporting of the Extension Period and will concern the classification into APTS_LT and FAS_LT.

If not otherwise stated, TFLs in the Placebo-controlled Period will be summarized by randomized treatment group and TFLs in the Extension Period will be summarized by treatment group in the extension (eptinezumab 300 mg or 100 mg).

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

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

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.

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

16.4 Patient Disposition

Patient disposition will be summarized based on the APRS and will include the analysis sets defined. The number of completed or withdrawn patients within each all-patient-treated set will also be included.

The number of patients who withdrew from treatment will be summarized for the Placebo-controlled Period and for the Extension Period by primary reason for withdrawal as well as by all reasons for withdrawal.

16.5 Demographics and Baseline Characteristics

Demographics (sex, age, and race), baseline characteristics (height, weight, and BMI), baseline efficacy variables, and other disease characteristics will be summarized based on the FAS.

16.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarized by anatomical therapeutic chemical (ATC) code and generic drug name in the Placebo-controlled Period and the Extension Period.

16.7 Exposure

Number of infusions in the Placebo-controlled Period (infusions at Visit 2 and visit 5), and number of infusions in the Extension Period (infusions at Visit 8, Visit 11, Visit 14, and Visit 17) will be summarized.

16.8 Efficacy Analyses

16.8.1 General Efficacy Analysis Methodology

All the statistical tests of the efficacy endpoints will be two-sided tests based on a 5% significance level and all confidence intervals (CIs) will be two-sided 95% CIs, unless otherwise specified.

16.8.2 Primary Analysis of the Primary Endpoint

The number of monthly migraine days (MMDs) Week 1-12 summarises diary data across Weeks 1 to 12. Details on derivation and imputations of days with missing or incomplete eDiary data will be described in the SAP.

Changes from baseline in MMDs at the 6 first 4-week intervals will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The analysis will be performed using all available monthly change scores for the first 6 months in the study. The model will include the following fixed effects: month (Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20, and Weeks 21-24), country, stratification factor (MHDs at baseline: ≤14/>14) and treatment as factors, baseline MMDs as a continuous covariate, treatment-by-month interaction, baseline score-by-month interaction, and stratum-by-month interaction. An unstructured variance structure will be used to model the within-patient errors. The mean differences between each dose of eptinezumab and placebo will be estimated based on the least squares means for the treatment-by-visit interaction in the MMRM model. The primary comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 1-12.

16.8.3 Sensitivity Analyses of the Primary Endpoints

The impact of missing data in the derivation of the primary endpoint (days with missing or incomplete information in the eDiary) will be evaluated by applying different methods of imputation. Details will be specified in the SAP.

16.8.4 Analysis of the Key Secondary Endpoints

- For the key secondary endpoints based on response rates, treatment effects compared to placebo will be analysed using logistic regression. The model will include baseline MMDs as a continuous covariate, and treatment and stratification (MHDs at baseline: ≤14 />14) as factors.
- The change from baseline in HIT-6 score for the Placebo-controlled Period will be analysed using a mixed model repeated measures (MMRM) including baseline HIT score as covariate, treatment, country, stratification factor (MHDs at baseline: ≤14 />14), and week as fixed factors. In addition, the model will include treatment-by-week interaction, baseline HIT-6 score-by-week interaction, and stratum-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Treatment effects will be calculated based on least squares means for the treatment-by-week interaction estimated at Week 12.
- Change from baseline in the number of MMDs (Weeks 13-24), will be analysed using the same MMRM methodology as for the primary endpoint. The comparisons will be the contrasts between each dose of eptinezumab and placebo averaged across Weeks 13-24.

16.8.5 Sensitivity Analyses of the Key Secondary Endpoints

Endpoints where data imputation is used, the impact of the imputations will be assessed in sensitivity analyses, applying different methods of imputation. Details will be specified in the SAP.

16.8.6 Testing Strategy

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

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

Step1

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

Step 2

Test the key secondary endpoint 50% responders for MMD (Weeks 1-12) for the 300 mg dose compared to placebo, using a significance level of α. Only if the p-value <α in favour of the

300 mg dose is the effect considered statistically significant and the testing continues with the next step.

Step 3

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

Step **4**

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

Step 5

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

Step 6

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

16.8.7 Analysis of the Secondary Endpoints

Analyses of continuous data based on diary data will use a similar model to the primary analysis, and continuous scale endpoints will be analysed by the same MMRM methodology as for HIT-6. Response variables will use similar analyses as the key secondary response

endpoints. The endpoints; patients with a migraine on the day after first dosing and 100% responders for MMDs and MHDs (Weeks 1-12) will be analysed using an extended Cochran-Mantel-Haenszel (CMH) test, adjusting for the stratification factor (MHDs at baseline: ≤14 />14).

16.8.8 Analysis of the Exploratory Endpoints

Analyses of continuous data based on diary data will use a similar model to the primary analysis, and continuous scale endpoints will be analysed by the same MMRM methodology as for HIT-6. Response variables will use similar analyses as the key secondary response endpoints.

16.8.9 Analysis of Subgroups

Details of subgroup analyses will be specified in the SAP.

16.9 Safety Analyses

16.9.1 Analysis of Adverse Events

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

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date and time of first infusion of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity during or after administration of the first dose of IMP. Adverse events, sorted by system organ class (SOC) and preferred term, will be summarized.

Allocation of TEAEs to Study Periods

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

16.9.2 Analysis of Other Safety Endpoints

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

Non-suicidal self-injury behaviour (considered separately) and no suicidal ideation or behaviour or the worst suicidal ideation or behaviour will be summarised for the double-blind treatment Period and the extension Period.

16.10 Sample Size and Power

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

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

The power was determined by simulating the testing strategy (10000 simulations) assuming normal distributions with similar mean and SD for continuous endpoints and similar success rates as the response variables in the Phase III studies for the corresponding population (EM or CM) without assuming the variables to be correlated. With 280 patients per treatment group, assuming that 40% of the patients will be from the EM population and 60% from the CM population, and that 2% of the patients do not have a post-baseline assessment of the primary endpoint, simulations show that the power for the test of the primary endpoint is approximately 94% for the comparison of 100 mg to placebo and 99% power for the comparison of 300 mg to placebo. The individual key secondary endpoints had a power of at least 68% for showing an effect, with a combined power of 58% for seeing an effect for all primary and key secondary endpoints and both doses in the testing strategy.

16.11 Statistical Analysis Plan

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

17 Clinical Study Report and Publications

17.1 Data Ownership

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

17.2 Clinical Study Report

For data collected in the Placebo-controlled Period a *Clinical Study Report* will be prepared by Regulatory Medical Writing, H. Lundbeck A/S. Upon completion of the study, an addendum to the *Clinical Study Report*, including the results from the Extension Period, will be produced.

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.

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).[50]

18 Indemnity and Insurance

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

19 Finance

19.1 Site Agreements

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

19.2 Financial Disclosure

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

19.3 Equipment

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

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Appendix I
Clinical Study Protocol
Authentication and Authorization

Clinical Study Protocol
Authentication and Authorization

Study title:	Interventional, randomized, double-blind, parallel-group, placebo-controlled study with an extension period to evaluate the efficacy and safety of eptinezumab for the prevention of migraine in patients with unsuccessful prior preventive treatments
Study No.:	18898A
Edition No.:	3.0
Date of edition:	30 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.

[redacted]

Authorization

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

[redacted]

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	See restrictions in use under *anti-migraine agents*. Other medication in the same class is allowed if prescribed for non-migraine indications.
Antihypertensives	See restrictions in use under *anti-migraine agents*. Other medication in the same class is allowed if prescribed for non-migraine indications.
Anti-impotence agents	Allowed if the dose has been stable for at least 12 weeks prior to the Screening Visit.
Anti-inflammatory agents	Allowed if prescribed for non-migraine indications, for example, low dose NSAIDs (acetylsalicylic acid) for cardiovascular disease prevention.
Antimigraine agents	Acute treatment of migraine (prescription or over-the-counter medication recommended by a healthcare professional) is allowed provided the dose has been stable for at least 12 weeks prior to the Screening Visit. Do not use preventive migraine treatments <1week prior to the Screening Visit and during the study. This includes daily use of: – beta-blockers: propranolol, metoprolol – anticonvulsants: topiramate, valproate or divalproex – tricyclics: amytriptyline – calcium channel blocker: flunarizine – angiotensin II receptor antagonist: candesartan – medication locally approved for prevention of migraine Other medications in the same classes above but not included in this list are allowed. Do not use oral anti-CGRPs for acute treatment <4 weeks prior to the Screening Visit and during the study. Do not use eptinezumab or other monoclonal antibody targeting the CGRP pathway <24 weeks prior to the Screening Visit and during the study. Patients who experienced failure on a previous treatment targeting the CGRP pathway are disallowed in the study. Do not use CNS- and migraine-related devices (neuromodulation, neurostimulation) or injectable therapy (trigger point injections, extracranial nerve blocks, or facet joint injections) <8 weeks prior to the Screening Visit and during the study. Do not use botulinum toxin for migraine or any other medical/cosmetic reason in the head and/or neck region <16 weeks prior to the Screening Visit and during the study. Do not use monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, or nimesulide <12 weeks prior to the Screening Visit and during the study.

Drug Class	Details
Hormones	Hormonal therapy (for example, contraceptives, hormone replacement therapy) is allowed provided the dose has been stable for at least 12 weeks prior to the Screening Visit.
Other interventions and devices	See restrictions for CNS- and migraine-related devices under *anti-migraine agents*. Non-pharmacological interventions (including CBT) are allowed provided the use has been stable for at least 12 weeks prior to the Screening Visit.
Sedatives/hypnotics	Limited use of the following is allowed provided a stable regimen (<4 days per month) has been maintained for at least 12 weeks prior to the Screening visit. These agents may be prescribed when considered medically indicated by the investigator during the study (including the screening period) providing its use does not exceed 4 days per month: – barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital). – prescription opiates (including single-ingredient or combination medications containing opiates, opioids, tramadol, or tapentadol).
Vaccinations	COVID-19 vaccinations are allowed during the study with the following guidance: – COVID -19 vaccination should not be given within ±3 days of the IMP administration. – If the patient has recently received a COVID-19 vaccine, the investigator should judge if the patient can be administered the IMP infusion at the scheduled visit based upon the patient's individual response to the COVID-19 vaccine. Other vaccination are allowed.