Electronic Signature Page

Full Title

Interventional, randomized, double-blind, parallel-group, placebo-controlled study of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with dual diagnosis of migraine and medication overuse headache

Short Title

20007A - Protocol - Edition 1.0

Study Number 20007A

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Clinical Study Protocol

Interventional, randomized, double-blind, parallel-group, placebo-controlled study of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with dual diagnosis of migraine and medication overuse headache

Eptinezumab

Study No.:	20007A (RESOLUTION)
EudraCT/IND No.:	2021-003049-40 (EU) / 114647 (US)
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Edition No.:	1.0 (the version No. in the footer is the system version No.)
Date of edition:	22 December 2021

Synopsis – Study 20007A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Eptinezumab
Study Title Interventional, randomized, double-blind, parallel-group, placebo-controlled study of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with a dual diagnosis of migraine and medication overuse headache	

Objectives and Endpoints **Objectives**	**Endpoints**
Primary Objective • To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH	**Primary endpoint:** – Change from baseline in the number of MMDs (Weeks 1-4) **Key secondary endpoints:** – Change from baseline in MMDs (Weeks 1-12) – Change from baseline in the number of MHDs (Weeks 1-4) – Change from baseline in MHDs (Weeks 1-12) – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 4) – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 12) – Change from baseline in average Daily Pain assessment score (Weeks 1-2) – Change from baseline in monthly days with acute medication use (Weeks 1-4) – Change from baseline in monthly days with acute medication use (Weeks 1-12) **Secondary endpoints:** – Not fulfilling the ICHD-3 diagnostic criteria for CM (Week 4, Week 12) – Not fulfilling the ICHD-3 diagnostic criteria for MOH (Week 4, Week 12) – Change from baseline in MMDs with use of acute medication (Weeks 1-12) – Change from baseline in monthly days with triptan or ergotamine medication use (Weeks 1-12) – Change from baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 1-12) – Change from baseline in monthly days with combination non-opioid analgesics medication use (Weeks 1-12) – Migraine on the day after dosing (Day 1) – Response: ≥50% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) – Response: ≥75% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) – Response: ≥50% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12) – Response: ≥75% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12)

Objectives and Endpoints (continued) **Objectives**	**Endpoints**
	Secondary endpoints (continued): – Change from baseline in rate of migraines with severe pain intensity (Weeks 1-4, Weeks 1-12) – Change from baseline in rate of headaches with severe pain intensity (Weeks 1-4, Weeks 1-12) – PGIC score at Week 4 and Week 12 – MBS score at Week 12 **Exploratory endpoints:** – Complete withdrawal of acute headache medication (Weeks 1-4, Weeks 5-8, Weeks 9-12)
Secondary Objectives • To evaluate the efficacy of eptinezumab as add-on to BI on health-related quality of life and work productivity	**Secondary endpoints** – Change from baseline to Week 4, and from baseline to Week 12 in the HIT-6 total score – Change from baseline to Week 4 and from baseline to Week 12 in the mMIDAS total score – Change from baseline to Week 4, and from baseline to Week 12 in the MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function) – Change from baseline to Week 4, and from baseline to Week 12 in the EQ-5D-5L VAS score – Migraine specific HCRU at Baseline and at Week 12 – Change from baseline to Week 12 in the WPAI:M sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment) – Change from baseline to Week 4, and from baseline to Week 12 in HADS - depression, and anxiety subscale scores – Change from baseline to Week 4, and from baseline to Week 12 in TSQM-9

Objectives and Endpoints (continued) **Objectives**	**Endpoints**
• To evaluate the efficacy of eptinezumab during the 12-week open-label extension period	– Change from baseline to Week 24 in the HIT-6 total score – Change from baseline to Week 24 in the mMIDAS total score – 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 – Migraine specific HCRU at Week 24 – Change from baseline to Week 24 in the WPAI:M sub-scores – Change from baseline to Week 24 in HADS - depression and anxiety subscale scores – PGIC score at Week 24 – MBS score at Week 24 – Change from baseline to Week 24 in TSQM-9 – Change from baseline to Week 24 in MMDs – Change from baseline to Week 24 in MHDs – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 24) – Change from baseline to Week 24 in monthly days with acute medication use – Change from baseline to Week 24 in average Daily Pain assessment score – Change from baseline to Week 24 in monthly days with triptan or ergotamine medication use – Change from baseline to Week 24 in monthly days with individual non-opioid analgesics or NSAID medication use
Exploratory Objectives • To investigate the efficacy of eptinezumab as add-on to BI on level of daily physical activity and sleep using a wearable digital device (subset)	**Exploratory Endpoints** – Change from baseline to Week 4 and Week 12 of passive registration of movement (actigraphy) (average per 28 days) • Minutes with light PA (11-50 a.U.) • Minutes with moderate PA (51-100 a.U.) • Minutes with intense PA (101-200 a.U.) • Minutes in rest period (range 0-300, 101: rest epoch) – Change from baseline to Week 4 and Week 12 in sleep metrics assessment as assessed by actigraphy (average per 28 days) • Total Sleep Time (minutes per night) • Sleep Efficiency (percentage per night) • Wake After Sleep Onset (minutes per night) • Sleep Onset Latency (minutes per night) All analyses will also be done by week, for example change from baseline to Week 1, baseline to Week 2, and baseline to Week 12.
• To investigate efficacy of eptinezumab as add-on to BI on the level of analgesic dependence	– Change from baseline to Week 12 in SDS:H score
Safety Objective • To evaluate the safety and tolerability of eptinezumab	**Safety Endpoints** – Adverse events – Absolute values and changes from baseline in vital signs – Potentially clinically significant vital signs changes

Study Methodology

- This is a phase 4, interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled study designed to demonstrate the efficacy and safety of add-on eptinezumab treatment to BI, performed at baseline, for the prevention of migraine and treatment of MOH in patients with a dual diagnosis of migraine and MOH. The 12-week placebo-controlled period will be followed by a 12-week open-label period where all patients will receive eptinezumab to provide further relief and gain exploratory data on the durability of a potential remission of the MOH and CM. The safety and tolerability of eptinezumab will be also further assessed in this open-label period.
- The target population for this study is defined as patients with a dual diagnosis of migraine and MOH and a level of disease activity matching the CM definition according to the IHS ICHD-3 guidelines. The medication overuse will be confirmed via prospectively collected information in the eDiary during the screening period.
- Patients will be instructed to stop medication overuse during a semi-structured educational conversation.
- Patients will be allowed use of medications (with restrictions for some of them) for acute and/or symptomatic treatment of headache (for example, paracetamol, NSAID, triptans, ergotamine, opioids, and/or combination analgesics) throughout the study. However, at the Baseline Visit they will be educated not to use acute medications.
- Eligible patients will be randomly allocated via a randomization system to one of the two treatment groups: BI and eptinezumab 100 mg, or BI and placebo, in a ratio of 1:1.
- Randomization will be stratified by country and number of previous preventive treatment failures (≤2; >2) occurring up to 5 years prior to Baseline Visit by using IRT system. Treatment failure is defined as treatment discontinuation due to lack of efficacy (no clinically meaningful improvement at the recommended or prescribed dose for at least 3 months), side effects, or general poor tolerability of the treatment.
- The total study duration from Screening Visit to Safety Follow-up Visit is approximately 36 weeks and includes a screening period (4 weeks), a placebo-controlled period (12 weeks), an open-label period (12 weeks), and a safety follow-up period (8 weeks).
- Patients will attend on-site visits at the Screening Visit, visits with IMP intravenous (IV) infusions (Baseline Visit and Week 12 Visit), and EoS Visit at Week 24. All other visits will be conducted as telephone or telemedicine visits.
- Patients will complete a daily headache eDiary from Screening Visit until EoS/Withdrawal Visit.
- Patients will receive BI and IMP (eptinezumab or placebo) at Baseline Visit during the placebo-controlled period and IMP (eptinezumab) at Week 12 Visit during the open-label period. IMP is administered by intravenous infusion over 30 minutes (with possibility to extend the intravenous infusion by 15 minutes).
- During the visits with IMP infusion, safety assessments will be performed before and after the IV infusion. The ePROs must be completed prior to the intravenous infusion. Patients must ensure to complete eDiary recording of headaches prior to the intravenous infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary).
- The primary outcome visit is at Week 4 during the placebo-controlled period.
- At designated sites, optional actigraphy assessments using a digital device will be performed on a consenting subset of patients. Patients can withdraw from these optional assessments without withdrawing from the main study.
- Patients will be scheduled for a Safety Follow-up Contact (at Week 32), 8 weeks after EoS Visit.
- Patients who withdraw their consent for study participation should be withdrawn from the study. However, all efforts should be done to keep the patients who interrupted/terminated their IMP infusion in the study and all assessments should be performed as described in the protocol. If patients want to withdraw from the study and thus not willing to attend the remaining visits as scheduled, they will be asked to attend a Withdrawal Visit as soon as possible and a Safety Follow-Up Contact, 20 weeks after last administration of IMP.
- The study design is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarized in Panel 2.

Number of Patients Planned

570 patients, recruited from specialist setting, are planned for randomization: 285 in the BI + eptinezumab 100 mg group and 285 in the BI + placebo group.

Target Patient Population

- Main Inclusion Criteria
  - The patient has a diagnosis of CM as defined by IHS ICHD-3 guidelines confirmed at the Screening Visit.
  - The patient has a history of migraine onset of at least 12 months prior to the Screening Visit.
  - The patient has ≥8 migraine days per month for each month within the past 3 months prior to the Screening Visit.
  - The patient has a diagnosis of MOH as defined by IHS ICHD-3 guidelines confirmed at the Screening Visit.
  - The patient has ≥15 headache days per month for each month within the past 3 months prior to the Screening Visit.
  - The patient has regular overuse of one or more drugs that can be taken for acute treatment of headache, for >3 months prior to the Screening Visit.
  - The patient has ≥15 to ≤26 headache days, of which ≥8 days were assessed as migraine days during the screening period, based on prospectively collected information in the eDiary.
  - The patient overuses drugs that can be taken for acute treatment of headache during the screening period, based on prospectively collected information in the eDiary.
  - The patient has a history of treatment failure with at least 1 preventive treatment within the last 5 years prior to the Screening Visit due to lack of efficacy (no clinically meaningful improvement at the locally recommended dose for at least 3 months).
  - 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 has had an onset of migraine diagnosis at ≤50 years of age.
  - The patient is aged ≥18 and ≤75 years at the Screening Visit.

- Main Exclusion Criteria
  - The patient has experienced failure on a previous preventive treatment targeting the CGRP pathway including gepants for acute or preventive use.
  - The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, chronic low back pain, and complex regional pain syndrome).
  - The patient has a diagnosis of acute or active temporomandibular disorders.
  - 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), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura and migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
  - The patient has psychosis, bipolar mania, dementia, or any other psychiatric conditions whose symptoms are not controlled or who has not been adequately treated for a minimum of 6 months prior to the Screening Visit.
  - The patient has a history of clinically significant cardiovascular disease, including uncontrolled hypertension, vascular ischaemia, or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).

Target Patient Population (continued)

- 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 exhaustive):
  - Disallowed: any investigational products within 30 days or 5 plasma half-lives (whichever is longer) before the Screening Visit. The following treatments are disallowed while the patient is under IMP (and can be prescribed after the patient has withdrawn the IMP treatment while still remaining in the study): eptinezumab or other mAb treatment targeting the CGRP pathway; oral CGRP antagonists for acute or preventive 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 restrictions: prescription or over-the-counter medication for preventive treatment of migraine prescribed or recommended by a health care 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.

IMP, Dose and Mode of Administration, and Reference Therapy

- Reference therapy: BI for MOH
  - BI is a semi-structured educational conversation with the purpose on helping the patients to reduce their MOH. The BI starts with five questions of the SDS:H (including an indication of the patient's willingness and confidence to change his/her medication overuse). Then patient is shown a short-structured scheme bases presentation either on a flip-over or slides with information about MOH and the association between medication overuse and chronic headache. The interview will end with an agreed plan on how to stop or reduce the medication overuse.

The intervention will take approximately 10 minutes to complete and is performed at Baseline Visit before IMP infusion.

- IMP
  - Dosage form
    - Eptinezumab – 100 mg, Concentrate for Solution for Infusion 100 mg/mL added to 100 mL of 0.9% normal saline
    - Placebo – 100 mL of 0.9% normal saline

The IMP will be administered at Baseline Visit and Week 12 Visit (Visit 5), by intravenous infusion over 30 minutes (+15 minutes).

Assessment Details

The assessments are summarized in Panel 2. Details for assessments that are non-standard or require more description are provided below:

- eDiary
  - Patients will complete a headache eDiary daily from the Screening Visit until the EoS/Withdrawal Visit. The eDiary consists of applications and reports which will be used to derive the migraine and headache endpoints, and medication use. The eDiary will be distributed to each patient at the Screening Visit after patient training on eDiary use by site staff. The eDiary data from the 28 days following the Screening Visit will be used to verify eligibility criteria, baseline migraine and headache values, and eDiary compliance. Ongoing evaluation of eDiary compliance will be performed by the study site based on eDiary reports.

Assessment Details (continued)

- HIT-6 (v1.0)
  - 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 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.
- mMIDAS
  - The mMIDAS is a self-reporting questionnaire designed to assess absenteeism (complete disability) and presenteeism (reduced participation) in several domains, including work, school, family, social, and leisure activities. The total number of days with disability is rated on a 4-point scale, from the lower total score that indicates a Little or No Disability; Mild Disability; Moderate Disability to the higher total score that indicates a Severe Disability. It takes approximately 5 to 10 minutes to complete the mMIDAS.
- 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 (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 to 10 minutes to complete the MSQ v2.1.
- PGIC
  - The PGIC is a single patient-reported item reflecting the patient's impression of change in their disease status since the Baseline Visit (that is, in relation to activity limitations, symptoms, emotions, and overall quality of life). The item is rated on a 7-point scale, where a high score indicate improvement (very much improved; much improved; minimally improved; no change; minimally worse; much worse; very much worse). It takes approximate 1 minute to complete the scale.
- MBS
  - The Investigator will verbally obtain the most bothersome symptom associated with the patient's migraines during the Screening Visit. The selected most bothersome symptom will be incorporated in the electronic version of the MBS (ePRO). Patients will be asked to rate the improvement in this symptom from screening on a 7-point scale identical to the scale used for the PGIC. The MBS areas include nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, and other. It takes less than 5 minutes to complete the MBS.
- HCRU
  - Migraine-specific health care resource utilization information will be collected in terms of outpatient health care professional visits, emergency room visits, hospital admissions, as well as duration of hospital stays. Clinical site personnel and patients will be instructed to capture utilization that takes place outside of visits associated with their participation in the clinical study. It takes approximately 5 minutes to complete the HCRU.
- WPAI:M
  - The WPAI 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:M assesses activities over the preceding 7 days and consists of 6 items: 1 item assess employment status, 3 items assess the number of hours worked, the number of hours missed from work due to the patient's condition, or due to other reasons, and 2 visual numerical scales to assess how much the patient's condition affects their productivity at work and their ability to complete normal daily activities. It takes approximately 5 minutes to complete the WPAI:M.

Assessment Details (continued)

- HADS
  - The HADS is a patient-rated scale designed to screen for anxiety and depressive states in non-psychiatric patients. The HADS consists of two sub-scales: the D-scale measures depression and the A-scale measures anxiety. Each sub-scale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each sub-scale ranges from 0 to 21 and are analysed separately. It takes approximately 5 to 10 minutes to complete the HADS.
- TSQM-9
  - The TSQM-9 is a generic questionnaire assessing the patient's satisfaction with the medication (IMP). The tool consists of 9 items addressing effectiveness, side effects, convenience, and overall satisfaction of the IMP. It takes approximately 5 minutes to complete the TSQM-9.
- Digital device, actigraphy (optional)
  - Actigraphy is a non-invasive way of monitoring activity and sleep. Actigraphy will be recorded using a wrist-worn device which continuously records physiological data. The device (actigraphy) assessment is a voluntary option for this study.
- SDS:H
  - The SDS:H is a patient reported scale, designed to assess dependency-like behaviour in patients with headache. The SDS:H is performed as a semi-structured interview, where the following questions will be addressed: 1) Do you think your use of headache medication was out of control? 2) Did the prospect of missing a dose make you anxious or worried? 3) Did you worry about your use of your headache medication? 4) Did you wish you could stop? 5) How difficult would you find it to stop or go without your headache medication? Each item is scored on a 4-point scale ranging from 0 (never/almost never, question 1-4, and not difficult, question 5) to 3 (always/nearly always, question 1-4, and impossible, question 5). It takes less than 5 minutes to complete the SDS:H.

Primary Estimand

Key elements of the primary estimand: the analyses of the primary endpoint aim to estimate "the treatment effect that is seen in the population, regardless of use of preventive migraine medication, assuming other anti-CGRP treatment is not available."

Estimands for the key secondary endpoints will be described in the SAP.

Complete set of attributes of the primary estimand:

- Intercurrent Events and Strategies
  - Initiation of a new preventive migraine medication other than anti-CGRP treatment, during the study period (Strategy: Treatment policy)
  - Use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication (Strategy: Hypothetical)
  - Interruption/termination of infusions (Strategy: Treatment policy)

- Treatment condition of interest
  - The treatment condition of interest is eptinezumab 100 mg compared to placebo provided as add-on to the BI

- Population
  - The population is the entire study population, that is, patients who suffer from migraine and MOH and who fulfil the inclusion and exclusion criteria.

- Variable
  - Change from baseline in MMDs (Weeks 1-4)

- Population-level summary
  - The population-level summary for the primary endpoint is the mean difference in the change from baseline in MMDs (Weeks 1-4) between patients on eptinezumab and placebo.

Statistical Methodology

- The following analysis sets will be used for the analyses:
  - APRS – all randomized patients
  - APTS – all patients in the APRS who received an infusion of the IMP in the placebo-controlled period
  - FAS – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
  - APTS-OL – all patients in the APRS who received an infusion of the IMP in the open-label period

The FAS will be used for all efficacy analyses in the placebo-controlled period, and the APTS will be used for all safety analyses in the placebo-controlled period, while the APTS-OL will be used for the safety and efficacy analysis of the open-label period.

- The main estimator for the primary estimand is defined as the estimated effect from the MMRM model described below:
  - The primary endpoint will be analysed using MMRM with the number of MMDs at baseline as a continuous covariate and including treatment group, month (Month 1: Weeks 1-4; Month 2: Weeks 5-8; Month 3: Weeks 9-12), country, and previous treatment failures (≤ 2; >2), as categorical variables. An interaction term between month and treatment as well as between month and number of MMDs at baseline will be included. The model will assume an unstructured covariance matrix to model the within patient variance. The statistical test will be based on the treatment contrast for change from baseline in MMDs (Weeks 1-4).

- The main estimator for each of the key secondary estimands is defined as the estimated effect from the analysis models described below:
  - All continuous key secondary endpoints addressing changes from baseline to Weeks 1 to 4 will be analysed using the same methodology as that described for the primary analysis.
  - All continuous key secondary endpoints addressing changes from baseline to Weeks 1 to 12 will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the estimated mean MMDs averaged over Weeks 1 to 4, Weeks 5 to 8, and Weeks 9 to 12.
  - Change from baseline in average Daily Pain will be analysed using ANCOVA with the average Daily Pain at baseline as a covariate and including treatment group, country, and previous treatment failures as categorical variables.
  - The binary key secondary endpoints will be analysed using logistic regression with baseline MMDs as a covariate and treatment and previous treatment failures (≤2, >2) as categorical variables.
- Sensitivity analyses of the primary endpoint will be described in the SAP.
- Sensitivity analyses of the key secondary endpoints will be described in the SAP.
- All statistical testing will be done two-sided, based on a 5% significance level.

Testing Strategy

For the primary endpoint (change from baseline in MMDs [Weeks 1-4]), test the hypothesis of no difference between the eptinezumab and placebo groups using a two-sided test on 5% significance level. If rejected and if the test shows a numerical advantage to eptinezumab, then continue to the first key secondary endpoint (change from baseline in MMDs [Weeks 1-12]).

On the first key secondary endpoint, test the hypothesis of no difference between the eptinezumab and placebo groups. If rejected and if the test shows a numerical advantage to eptinezumab, then continue to the second key secondary endpoint (change from baseline in MHDs [Weeks 1-4]). This continues through the list of key secondary endpoints (change from baseline in MHD [Weeks 1-12], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Week 4], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Week12], change from baseline in average Daily Pain assessment score [Weeks 1-2], change from baseline in monthly days with acute medication use [Weeks 1-4], change from baseline in monthly days with acute medication use [Weeks 1-12]), until an endpoint fails to reach significance.

Sample Size Considerations

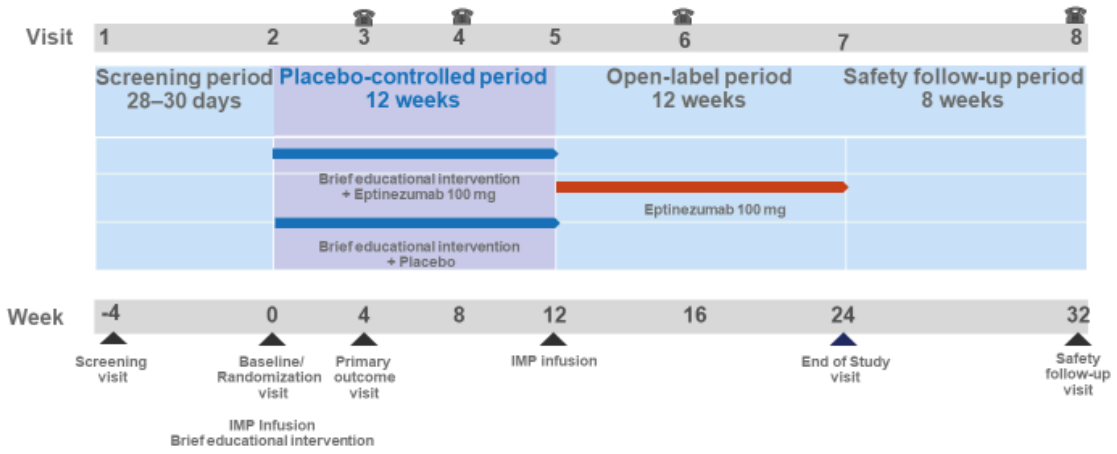
It is assumed that the treatment effect of eptinezumab 100 mg compared to placebo in change from baseline in MMDs (Weeks 1-4) will be -1.5 MMDs. The difference between eptinezumab 100 mg and placebo was -2.0 in Study 011, a study that did not include education on MOH, after 4 weeks and –3.1 in the subgroup of patients with CM and MOH. The difference between withdrawal from treatment with and without preventive treatment was –1.7 and –1.4 days after 2 and 4 months.

The SD is assumed to be 6.2, based on the averaged SD across treatment groups in the MOH subgroup of Study 011 on the change from baseline in MMDs (Weeks 1-4).

Based on the assumed effect size and SD, using a two-sided test on the 5% significance level, 270 patients per treatment group will provide 80% power for showing an effect on the primary endpoint. Assuming 5% of patients will not contribute data to the analysis, 285 patients randomized per treatment group or 570 patients randomized in total will be needed.

Sample size re-assessment will be conducted on blinded data when approximately 70% of the patients have been randomized.

Panel 1 Study Design



IMP = investigational medicinal product

Panel 2 Study Procedures and Assessments

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralized[c]	Withdrawal[d]
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoS Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
Screening and Baseline Procedures and Assessments									
Signed informed consent (including digital wearables)	√								
Demographics (age, sex, and race)	√								
Diagnosis (migraine and MOH)	√								
Disease-specific history[e]	√								
Relevant history (social, medical, psychiatric, neurological)	√								
Previous migraine and preventive medication use[e] including treatment failures	√								
Recent medication (prescription and non-prescription: traditional herbal medicines, non-pharmacological interventions, vitamins and mineral supplements)	√								
Height and weight	√								

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralized[c]	Withdrawal[d]
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoS Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
Examinations (physical, neurological)	√								
Blood sampling for eligibility (including serology and other screening, for example β-HCG)	√								
Urine drug and alcohol screen	√								
ECG	√								
C-SSRS[f]	√								
Inclusion/exclusion criteria	√	√							
Signs and symptoms present at Screening and/or Baseline (before IMP intake) (recorded on an *Adverse Event Form*)	√	√							
Randomization		√							
Efficacy Assessments (eDiary and ePROs[g])[h]									
eDiary recording[i]	√	√[j]	√	√	√[j]	√	√[k]		√[k]
eDiary compliance check[l]		√	√	√	√	√	√		
PGIC			√		√[j]		√		√
MBS	√	√[j]			√[j]		√		√
HADS		√[j]	√		√[j]		√		√
Digital device (optional)[m]	√	√	√	√	√[n]				√[n]
Pharmacoeconomic Assessments (ePROs[g])[h]									
HIT-6		√[j]	√		√[j]		√		√
mMIDAS		√	√		√		√		√
MSQ v2.1		√[j]	√		√[j]		√		√
EQ-5D-5L		√[j]	√		√[j]		√		√
HCRU		√[j]	√		√[j]		√		√
WPAI:M		√[j]	√		√[j]		√		√
TSQM-9		√[j]	√		√[j]		√		√
Safety Assessments									
Adverse events		√[o,p,q]	√	√	√[o,p,q]	√	√	√	√
Vital signs (including body temperature)	√	√[p,q]			√[p,q]		√		√
Other Study Procedures and Assessments									
Brief educational intervention[r], including SDS:H		√							
SDS:H					√				

Visit Name	Screening	Placebo-controlled Period			Open-label Period			Safety Follow-up Decentralized[c]	Withdrawal[d]
		Baseline + IMP	PO Visit, Decentralized[c]	Decentralized[c]	IMP	Decentralized[c]	EoS Visit		
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**WD**
End of Week[a]	**-4**	**0**	**4**	**8**	**12**	**16**	**24**	**32**	
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	
IMP administered (intravenous infusion)[s]		√[o,t]			√[o,t]				
IMP accountability[u]		√			√				
Concomitant medication (prescription and non-prescription: traditional herbal medicines, non-pharmacological interventions, vitamins, and mineral supplements)		√[q]	√	√	√[q]	√	√	√	√
Substance use (alcohol, tobacco, caffeine, marijuana)	√	√	√	√	√				√[v]
eDiary training[h]	√								
ePRO training[h]	√								
eDiary closeout[k]							√		√
Pregnancy test[w]	√	√			√		√		√

β-HCG = human chorionic gonadotropin; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EoS = end of study; eDiary = electronic diary; ePRO = electronic patient-reported outcome; EQ-5D-5L = Euroqol 5 Dimensions; HADS = Hospital Anxiety and Depression Scale; HCRU = Health Care Resource Utilization; HIT-6 = Headache Impact Test; IMP = investigational medicinal product; MBS = Most Bothersome Symptom; mMIDAS = modified Migraine Disability Assessment; MOH = medication overuse headache; MSQ v2.1 = Migraine-Specific Quality of Life Questionnaire Version 2.1; PGIC = Patient Global Impression of Change; PO = primary outcome; SDS: H = Severity of Dependence Scale Adapted for Headache; TSQM-9 = Treatment Satisfaction Questionnaire for Medicine – 9 items; WD = withdrawal; WPAI:M = Work Productivity and Activity Impairment questionnaire, Migraine version

a. All assessments may be completed over a maximum of 2 consecutive days with the exception of ePROs (see footnote g below); if so, the first day is considered the "visit" day according to the schedule.
b. If the date of an on-site visit or decentralized contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit. In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended by an extra period of seven days with approval from the sponsor (the medical expert at H. Lundbeck A/S or the CRO's medical monitor) based on the provided rationale.
c. For decentralized visits, the patient will be contacted for eDiary compliance check, to ensure that the selected assessments have been completed and for collection of relevant information such as adverse events and concomitant medications.
d. Patients who withdraw their consent for study participation should be withdrawn from the study. However, all efforts should be done to keep the patients who interrupted/terminated their IMP infusion in the study and all assessments should be performed as described in the protocol. If patients want to withdraw from the study and thus not willing to attend the remaining visits as scheduled, they will be asked to attend a Withdrawal Visit as soon as possible and a further Safety Follow-up Visit at 20 weeks after administration of IMP.

e. Patients' available adequately documented records of migraine and MOH history and previous migraine preventive medication use (including treatment failures) within the 5 years prior to the Screening Visit. See chapter 12 for definition of adequately documented records.
f. The C-SSRS at Screening Visit will be administered by the authorized rater at the clinical site.
g. ePROs scheduled at Baseline Visit (Visit 2) and Week 12 Visit (Visit 5) must be completed in the clinical site on the visit date and before the infusion. ePROs which are scheduled in alignment with the Withdrawal Visit can be completed in the clinical site or in a remote setting within 3 days prior to the scheduled on-site visit date. ePROs which are scheduled in alignment with a decentralized contact must be completed in a remote setting and can be completed on the day or within 3 days prior to the scheduled decentralized contact date.
h. At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary and ePROs. Details will be provided in a separate user manual.
i. The eDiary assessments will be completed in the remote setting on a daily basis from Screening to EoS.
j. On the Baseline Visit and Week 12 Visit day, patients must complete the ePRO entries prior to infusion. Patients must ensure to complete eDiary recording of headaches that ended prior to infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary).
k. The eDiary closeout will take place at EoS Visit/Withdrawal Visit while the patient is at the clinical site. Details will be provided in a separate user manual.
l. In addition to the eDiary compliance checks performed at the defined on-site visits and decentralized contacts, ongoing evaluation of eDiary compliance will be performed by the site (based on eDiary reporting) and more frequent contact with patients may be needed in case of non-compliance.
m. At designated sites, the patients undergoing the additional actigraphy assessments must provide a signed digital device Informed Consent Form.
n. Hand in of Digital device. Patients undergoing the additional actigraphy assessments who drop out from the study before Visit 5 must hand in the device at the Withdrawal Visit.
o. Infusion Related Reactions must be checked as part of the overall adverse event collection, during/after infusion and before the patient is discharged from the site.
p. Infusion must be preceded by the assessment of vital signs including body temperature, concomitant medications, and adverse events.
q. Vital signs including body temperature and adverse events must be checked after infusion.
r. The brief educational intervention must take place prior to IMP infusion.
s. 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.
t. Patients must be monitored during and after the infusion in accordance with usual clinical practice.
u. A designated unblinded CRA is responsible for the IMP accountability.
v. Substance use will only be collected if the patient withdraws during the placebo-controlled period.
w. For women of childbearing potential, pregnancy test at the Screening Visit is to be conducted using serum β-HCG. At all other visits, where this is applicable the urine pregnancy testing will be performed using a urine stick test and in case of a positive finding, further confirmatory testing will be performed via serum β-HCG.

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HCV	hepatitis C virus antibody
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS-OL	all-patients-treated set Open-Label
AST	aspartate aminotransferase
a.U.	arbitrary unit
AUC	area under the concentration-time curve
BI	brief educational intervention
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 2019
CRA	clinical research associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EC	ethics committee
eCOA	electronic clinical outcome assessment
EM	episodic migraine
EMA	European Medicines Agency
EoS	End-of-Study
FAS	full-analysis set
ePRO	electronic patient-reported outcome
EQ-5D-5L	Euroqol 5 Dimension – 5 Levels
US FDA	United States Food and Drug Agency
HADS	Hospital Anxiety and Depression Scale
HCG	human chorionic gonadotropin
HCRU	Health Care Resources Utilization
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
ICHD	International Classification of Headache Disorders

IHS	International Headache Society
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
IRR	infusion related reaction
mAb	monoclonal antibody
MBS	Most Bothersome Symptom
MHD	monthly headache day
MMD	monthly migraine day
mMIDAS	modified Migraine Disability Assessment
MMRM	Mixed Models Repeated Measurements
MOH	medication overuse headache
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire, Version 2.1
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PA	physical activity
PGIC	Patient Global Impression of Change
QP	qualified person
QT_{cF}	heart-rate corrected QT interval using Fridericia's correction formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDS:H	Severity Dependence Scale adapted for headache
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
TSQM-9	Treatment Satisfaction Questionnaire for Medicine – 9 items
VAS	Visual Analogue Scale
WPAI:M	Work Productivity and Activity Impairment Questionnaire, Migraine version

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] 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 second leading cause of disability worldwide.[2,3]

MOH is the development of a new type of headache, or significant worsening of pre-existing headache, resulting from frequent and excessive intake of medications for the acute treatment of headache[1]. MOH prevalence is estimated at 1% to 2% worldwide but varies from country to country (range 0.5% to 7%). Acute medications (for treatment of a migraine / headache once it begins) involved in MOH vary with country and over time.[4,5] MOH is defined as the combination of chronic headache and overuse of analgesics and/or acute migraine medication (use of paracetamol and NSAID ≥15 days a month, or triptans, ergotamine, opioids, combination-analgesics, or any combination of drug classes ≥10 days a month). In fact, medication overuse is considered the most central factor for chronification of migraine, and 40% to 70% of patients with CM also fulfil the diagnostic criteria for MOH.

The condition of MOH with underlying migraine may be treated by education of patients to stop/reduce acute medication or institute an acute medication withdrawal for 8 weeks or combine education or withdrawal with other preventive medication targeting the underlying migraine. However, these treatment strategies often lead to initial severe discomfort in terms of worsening in headache (the so-called rebound headache), and withdrawal symptoms (such as, nausea, vomiting, hypotension, tachycardia, sleep disturbance, restlessness, anxiety, and nervousness). These symptoms, lasting approximately 2 to 3 weeks[6], may be attenuated by rescue medication and anti-emetics, but there is no consensus on rescue medication. Thus, potentially avoiding this initial period of discomfort for the patients could ensure a successful stop of acute medication overuse. Furthermore, in many clinics there is immense resistance from health care providers against this medication withdrawal because it often leads to a need for hospitalization for a number of weeks, due to severity of the rebound headaches and the related anxiety from the patients. After successful medication withdrawal, patients will still suffer from their primary headache and although some patients get relief and transform from their CM into an EM, they still need treatment for their migraine.

Several clinical studies have been conducted to provide evidence that combination of preventive medication and withdrawal of overused medication is the most optimal treatment; however, no significant results have been obtained.[7,8] Thus, this evidence is lacking and in current guidelines, no clear advice is given. The previous studies that have investigated oral preventive medications or botox were limited in sample size and were mostly single-centre studies.[9] None of the new CGRP mAbs have been investigated as add-on treatment to education of treatment management or of medication withdrawal. Therefore, it is of high

clinical relevance to explore if education about the cause of MOH aiming to eliminate the medication overuse would benefit from combination with a preventive treatment that has rapid onset of action and long-lasting effect. For this purpose, the intravenously administered CGRP mAb, eptinezumab, with an early onset may be a strong candidate due to its pharmacokinetic profile (specifically, its immediate high bioavailability and its ability to reach steady state within 30 minutes of administration), potentially offering patients an effective preventive treatment that in combination with motivational education could secure a successful and lasting relief from MOH by terminating the acute medication overuse.

There is no gold standard for this type of patient education of treatment management or of medication withdrawal. While current guidelines recommend that patients with MOH should be managed by a multidisciplinary team of neurologists or pain specialists and behavioural psychologists, these resources are not available in most headache clinics and only few clinics are able to provide inpatient care for the patients to the often-necessary level of intervention to ensure a successful outcome. BI as a patient education tool have been investigated in a study with general practitioners in Norway with promising results[7]. As it only takes on average 10 minutes to conduct, it would be feasible to provide BI at most headache clinics when combined with a fast--onset modern preventive therapy.

CGRP is known 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 CNS.[10,11] Studies in animals and humans indicate that the trigeminal ganglion and its nucleus caudalis are likely to be sites of action of CGRP in migraine. In addition, CGRP is expressed at low level in many locations within the CNS, including regions that may be relevant to migraine pain.[12,13] During migraine attacks, there is an increase in the plasma levels of CGRP in the external jugular vein.[14] In addition, intravenous 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.[15] CGRP dilates intracranial and extracranial blood vessels, and regulates mast cell degranulation, which during migraine, leads to the secretion of vasoactive, proinflammatory, and neurosensitizing mediators, thereby contributing to migraine pathogenesis.[16,17]

A large body of evidence has established the CGRP pathway as a target for the treatment of migraine. Studies with mAbs targeting CGRP or the CGRP receptor have shown that inhibition of CGRP is efficacious in the treatment of chronic and episodic migraine.[18,19,20]

Eptinezumab is a humanised mAb that binds and blocks the action of CGRP and is approved by several medical agencies, including the US FDA and EMA, as the first and only intravenous preventive treatment for migraine. Eptinezumab addresses an unmet medical need of patients who require preventive treatment of migraine with an early onset of effect. Eptinezumab is administered by intravenous infusion every 12 weeks offering a route of drug administration with 100% bioavailability that allows for rapid CGRP inhibition, which has been associated with a clinically meaningful migraine preventive effect as soon as the day following the first infusion and pain relief from ongoing attacks within hours (CSR ALD403-CLIN-015/18903A). Eptinezumab intravenous infusion administered every 12 weeks by a health care professional helps to ensure treatment adherence and delivery of a

known quantity of drug with each dose. Results from two placebo--controlled, phase 3 studies showed that eptinezumab led to significant reductions in the number of MMDs in patients with EM (ALD403 CLIN-006)[21] and CM (ALD403-CLIN-011).[22] Furthermore , treatment with eptinezumab has been associated with a sustained efficacy throughout the treatment period and an acceptable tolerability profile with low incidences of study drug withdrawal due to adverse events.

The following sections provide a brief overview of the nonclinical and clinical data currently available for eptinezumab. Refer to the current version of the Investigator's Brochure[23] for more detailed information.

1.1.2 Nonclinical Data

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

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

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

Overall, following intravenous administration in the nonclinical studies, eptinezumab exposure was generally dose proportional, and the plasma-concentration profiles were consistent for intravenous administration with the rapid achievement of C_{max} followed by a mono-exponential decline. The volume of distribution for eptinezumab is generally limited to the vascular compartment.[23]

Eptinezumab is unlikely to interact directly with deoxyribonucleic acid or other chromosomal material, and under ICH S6(R1) guidance, evaluations for potential genotoxicity were considered unnecessary and were not performed for eptinezumab. Based on extensive evaluation of the literature related to inhibition of CGRP, angiogenesis, and tumour growth as

well as the absence of eptinezumab-related proliferative findings from long-term studies in monkeys, no further nonclinical studies addressing the carcinogenic risk are considered necessary.

Eptinezumab is being developed for the prevention of migraine, and a significant proportion of migraineurs are women of childbearing potential.[24] 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. No effects on male or female reproductive function or performance, fertility, or early embryonic development in rats were observed. No parental effects or evidence of embryo-lethality, fetotoxicity, or teratogenicity in rats or rabbits were observed. There were no effects on the survival, physical development, behaviour, or reproductive performance of the first filial generation in the pre- and postnatal development study in rats.

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

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

1.1.3 Clinical Data

The clinical program of eptinezumab is composed of six completed studies to date; 4 studies are placebo-controlled (phase 1b study in frequent EM (ALD403-CLIN-002),[26] phase 2 study in CM (ALD403-CLIN-005),[27] phase 3 study in frequent EM (ALD403-CLIN 006),[21] phase 3 study in CM (ALD403-CLIN-011)[22], one study is open-label (phase 3 study in CM (ALD403-CLIN-013))[28,29], and a Phase 3 study (18903A)[30] to assess treatment of eptinezumab in patients experiencing an acute attack of migraine.

Eptinezumab is administered by 30-minute intravenous infusion, which bypasses extravascular absorption routes and renders 100% bioavailability. The time required to achieve therapeutic concentrations for eptinezumab is rapid and C_{max} is typically observed at the end of infusion. The low plasma clearance (0.15 L/d) and protracted terminal-elimination half-life of 27 days for eptinezumab support a sustained duration of effect and infrequent, once every 12 weeks dosing. The mean accumulation ratios based on C_{max} and AUC during the first dosing interval are 1.08 and 1.15, respectively.

Eptinezumab is not metabolized by cytochrome P450 enzymes. Therefore, interactions by eptinezumab with concomitant medications that are substrates, inducers, or inhibitors of

cytochrome P450 enzymes are considered unlikely.[31] Nevertheless, the co-administration of eptinezumab in combination with sumatriptan was investigated in Study ALD403-CLIN-001.[23] The co-administration of sumatriptan did not appear to alter the single dose PK of eptinezumab. Similarly, the PK of sumatriptan was not impacted upon by the co-administration of eptinezumab.

Results from the two pivotal, placebo-controlled, phase 3 studies showed that eptinezumab at doses of 100 mg or 300 mg administered by intravenous infusion every 12 weeks (2 infusions) led to significant reductions in MMDs in patients with EM or CM (ALD403-CLIN-006 and ALD403-CLIN-011).[21,22] 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. Furthermore, subgroup analyses showed that the reduction in MMDs seen with eptinezumab compared to placebo was also present in the distinct subpopulation of patients with the dual diagnosis of migraine and MOH. Post-hoc analyses indicated that in the subgroup of patients with MOH, eptinezumab also had advantages over placebo in the 50% and 75% response rates for Weeks 1 to 12, for both doses ($p<0.05$). The early onset of eptinezumab 100 mg has been further established by the results from the recently completed Study 18903A (CSR ALD403-CLIN-015/18903A). The results, evaluated within 48 hours after start of infusion, demonstrated that patients receiving an intravenous infusion of eptinezumab 100 mg during an ongoing migraine attack achieved statistically significant shorter time to freedom from headache pain ($p = 0.0006$). The median time to freedom from headache pain was 4 hours for patients receiving eptinezumab 100 mg and 9 hours for patients receiving placebo. Similarly, the results also showed that patients receiving eptinezumab had a statistically significantly shorter time to absence of their MBS ($p <0.0001$) compared to patients receiving placebo, a median time of 2 hours versus 3 hours. The key secondary endpoints, headache pain freedom and absence of MBS 2 hours post-dose, were also statistically significantly in favour of eptinezumab (23.5% *versus* 12% [$p = 0.0009$] and 55.5% *versus* 35.8% [$p <0.0001$], respectively). Furthermore, eptinezumab 100 mg was also statistically significantly ($p <0.001$) better than placebo on all the secondary endpoints included in the testing hierarchy in Study 18903A (headache pain freedom and absence of MBS 4 hours post-dose as well as on the use of acute medication within 24 hours). Median time to next migraine was 10 days with eptinezumab *versus* 5 days with placebo ($p <0.001$).

The safety of eptinezumab has been evaluated in more than 2500 patients with migraine. Nasopharyngitis and hypersensitivity reactions, including anaphylactic reactions and fatigue are considered adverse drug reactions for eptinezumab. In the pivotal phase 3 studies (ALD403-CLIN-006 and ALD403-CLIN-011) hypersensitivity reactions were reported with multiple related adverse event terms, such as hypersensitivity, angioedema, urticaria, flushing/hot flush, rash, and pruritus. These events were reported in approximately 4% of

patients on 300 mg eptinezumab, 3% of patients on 100 mg eptinezumab, and 1% of patients on placebo. Furthermore, approximately 3% of patients on eptinezumab and 2% of patients on placebo in the placebo-controlled clinical trials experienced fatigue. Fatigue was most frequent on the day of the first infusion. Following the first week and with subsequent infusions, fatigue was reported in lower incidences and the incidences were comparable to placebo. The majority of these adverse events were categorized as *mild* to *moderate*, and most hypersensitivity reactions occurred during the infusion. Serious hypersensitivity reactions have been reported, including anaphylactic reactions on rare occasions. In most cases, the events developed during or within minutes of the infusion and patients recovered following drug discontinuation and adequate treatment.

Long-term safety data with eptinezumab is limited; however, 128 patients 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 favourable risk-benefit profile based on review of nonclinical, clinical, and scientific literature data.

1.2 Rationale for the Study

Eptinezumab is approved for migraine prevention and s substantial proportion of migraine patients have a dual diagnosis of migraine and MOH. These patients generally constitute the most burdensome population, accounting for approximately 80% of all health care costs generated by the patients with CM.[32]

MOH is a global health problem with a prevalence in the general adult population of different countries ranging from 0.5% to 7.6%. Robust data from Scandinavia indicate a prevalence of 1% to 2%, representing around 50% of all patients with chronic daily headache.[6] There is a substantial proportion of patients with a dual diagnosis of migraine and MOH worldwide[5,33] who do not respond to, or cannot tolerate, existing treatments. None of the new CGRP mAbs have been investigated as add-on treatment to education or medication withdrawal. Therefore, it is of high clinical relevance to explore if BI would benefit from combination with a preventive treatment that has rapid onset of action and long-lasting effect.

This study is a placebo-controlled study in patients with a dual diagnosis of migraine and MOH. The study is intended to evaluate the effect on MMDs, of eptinezumab as add-on treatment to BI, for the prevention of migraine and treatment of MOH in patients with a dual diagnosis of migraine and MOH.

2 Objectives, Endpoints, and Estimands

The study objectives, endpoints, and estimands are summarized in Panel 3.

Panel 3 Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH	**Primary Endpoint:** – Change from baseline in the number of MMDs (Weeks 1-4) **Key Secondary Endpoints:** – Change from baseline in MMDs (Weeks 1-12) – Change from baseline in the number of MHDs (Weeks 1-4) – Change from baseline in MHDs (Weeks 1-12) – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 4) – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 12) – Change from baseline in average Daily Pain assessment score (Weeks 1-2) – Change from baseline in monthly days with acute medication use (Weeks 1-4) – Change from baseline in monthly days with acute medication use (Weeks 1-12) **Secondary Endpoints:** – Not fulfilling the ICHD-3 diagnostic criteria for CM (Week 4, Week 12) – Not fulfilling the ICHD-3 diagnostic criteria for MOH (Week 4, Week 12) – Change from baseline in MMDs with use of acute medication (Weeks 1-12) – Change from baseline in monthly days with triptan or ergotamine medication use (Weeks 1-12) – Change from baseline in monthly days with individual non-opioid analgesics or NSAID medication use (Weeks 1-12) – Change from baseline in monthly days with combination non-opioid analgesics medication use (Weeks 1-12) – Migraine on the day after dosing (Day 1) – Response: ≥50% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) – Response: ≥75% reduction from baseline in MMDs (Weeks 1-4, Weeks 1-12) – Response: ≥50% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12) – Response: ≥75% reduction from baseline in MHDs (Weeks 1-4, Weeks 1-12) – Change from baseline in rate of migraines with severe pain intensity (Weeks 1-4, Weeks 1-12) – Change from baseline in rate of headaches with severe pain intensity (Weeks 1-4, Weeks 1-12) – PGIC score at Week 4 and Week 12 – MBS score at Week 12 **Exploratory Endpoint:** – Complete withdrawal of acute headache medication (Weeks 1-4, Weeks 5-8, Weeks 9-12)

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary Estimand
Key elements to the primary estimand: the analyses of the primary endpoint aim to estimate “the treatment effect that is seen in the population, regardless of the use of preventive migraine medication, assuming other anti-CGRP treatment is not available.”
Estimands for the key secondary endpoints will be described in the SAP.

Complete set of attributes of the primary estimand:
• Intercurrent Events and Strategies
– Initiation of a new preventive migraine medication other than anti-CGRP treatment, during the study period (Strategy: Treatment policy)
– Use of disallowed anti-CGRP medication other than eptinezumab as preventive migraine medication (Strategy: Hypothetical)
– Interruption/termination of infusions (Strategy: Treatment policy)

• Treatment condition of interest
– The treatment condition of interest is eptinezumab 100 mg compared to placebo provided as add-on to the BI.

• Population
– The population is the entire study population, that is, patients who suffer from migraine and MOH and who fulfil the inclusion and exclusion criteria.

• Variable
– Change from baseline in MMDs (Weeks 1-4)

• Population-level summary
– The population-level summary for the primary endpoint is the mean difference in the change from baseline in MMDs (Weeks 1-4) between patients on eptinezumab and placebo.</td></tr>
<tr><td>Secondary Objectives:
• To evaluate the efficacy of eptinezumab as add-on to BI on health-related quality of life and work productivity</td><td>Secondary Endpoints:
– Change from baseline to Week 4 and from baseline to Week 12 in the HIT-6 total score
– Change from baseline to Week 4 and from baseline to Week 12 in the mMIDAS total score
– Change from baseline to Week 4 and from baseline to Week 12 in the MSQ v2.1 sub-scores (Role Function-Restrictive, Role Function-Preventive, Emotional Function)
– Change from baseline to Week 4,andfrom baseline to Week 12 in the EQ-5D-5L VAS score
– Migraine specific HCRU at Baseline and at Week 12
– Change from baseline to Week 12 in the WPAI:M sub-scores (Absenteeism, Presenteeism, Work productivity loss, Activity impairment)
– Change from baseline to Week 4, and from baseline to Week 12 in HADS - depression, and anxiety subscale scores
– Change from baseline to Week 4 and from baseline to Week 12 in TSQM-9</td></tr>
</table>

Objectives	Endpoints
• To evaluate the efficacy of eptinezumab during the 12-week open-label extension period	– Change from baseline to Week 24 in the HIT-6 total score – Change from baseline to Week 24 in the mMIDAS total score – Change from baseline to Week 24 in the MSQ v2.1 sub-scores – Change from baseline Week 24 in the EQ-5D-5L VAS score – Migraine specific HCRU at Week 24 – Change from baseline to Week 24 in the WPAI:M sub-scores – Change from baseline to Week 24 in HADS - depression and anxiety subscale scores – PGIC score at Week 24 – MBS score at Week 24 – Change from baseline to Week 24 in TSQM-9 – Change from baseline to Week 24 in MMDs – Change from baseline to Week 24 in MHDs – Not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH (Week 24) – Change from baseline to Week 24 in monthly days with acute medication use – Change from baseline to Week 24 in average Daily Pain assessment – Change from baseline to Week 24 in monthly days with triptan or ergotamine medication use – Change from baseline to Week 24 in monthly days with individual non-opioid analgesics or NSAID medication use
Exploratory Objectives: • To investigate the efficacy of eptinezumab as add-on to BI on level of daily physical activity and sleep using a wearable digital device (subset) • To investigate efficacy of eptinezumab as add-on to BI on the level of analgesic dependence	**Exploratory Endpoints:** – Change from baseline to Week 4 and Week 12 of passive registration of movement (actigraphy) (average per 28 days) - Minutes with light PA (11-50 a.U.) - Minutes with moderate PA (51-100 a.U.) - Minutes with intense PA (101-200 a.U.) - Minutes in rest period (range 0-300, 101: rest epoch) – Change from baseline to Week 4 and Week 12 in sleep metrics assessment as assessed by actigraphy (average per 28 days) - Total Sleep Time (minutes per night) - Sleep Efficiency (percentage per night) - Wake After Sleep Onset (minutes per night) - Sleep Onset Latency (minutes per night) All analyses will also be done by week, for example change from baseline to Week 1, from baseline to Week 2, and from baseline to Week 12. – Change from baseline to Week 12 in SDS:H score
Safety Objective: • To evaluate the safety and tolerability of eptinezumab	**Safety Endpoints:** – Adverse Events – Absolute values and changes from baseline in vital signs – Potentially clinically significant vital signs changes

3 Study Design

3.1 Overview of the Study Design

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

This is a phase 4, interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled study designed to demonstrate the efficacy and safety of add-on eptinezumab treatment to BI, performed at baseline, for the prevention of migraine and treatment of MOH in patients with a dual diagnosis of migraine and MOH.

The 12-week placebo-controlled period will be followed by a 12-week open-label period where all patients will receive eptinezumab to provide further relief and gain exploratory data on the durability of a potential remission of the MOH and CM. The safety and tolerability of eptinezumab will be also further assessed in this open-label period.

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

An overview of the study is presented in Panel 1.

The target population for this study is defined as patients with a dual diagnosis of migraine and MOH and a level of disease activity matching the CM definition, according to the IHS ICHD-3 guidelines.[1] The medication overuse will be confirmed via prospectively collected information in the eDiary during the screening period.

Patients will be instructed to stop medication overuse during a semi-structured educational conversation.

Patients will be allowed use of medications (with restrictions for some of them) for acute and/or symptomatic treatment of headache (for example, paracetamol, NSAID, triptans, ergotamine, opioids, and/or combination analgesics) throughout the study. However, at the Baseline Visit they will be educated not to use acute medications.

Eligible patients will be randomly allocated via a randomization system to one of the two treatment groups: BI and eptinezumab 100 mg, or BI and placebo, in a ratio of 1:1.

Randomization will be stratified by country and number of previous preventive treatment failures (≤2; >2) occurring up to 5 years prior to Baseline Visit by using the IRT system. Treatment failure is defined as treatment discontinuation due to lack of efficacy (no clinically meaningful improvement at the recommended or prescribed dose for at least 3 months), side effects, or general poor tolerability of the treatment.

The total study duration from Screening Visit to Safety Follow-up Contact is approximately 36 weeks and includes a screening period (4 weeks), a placebo-controlled period (12 weeks), an open-label period (12 weeks), and a safety follow-up period (8 weeks).

Patients will attend on-site visits at Screening Visit, visits with IMP intravenous infusions (Baseline Visit and Week 12 Visit), and EoS Visit at Week 24. All other visits will be conducted as telephone or telemedicine visits.

Patients will complete a daily headache eDiary from Screening Visit until EoS/Withdrawal Visit.

Patients will receive BI and IMP (eptinezumab or placebo) at Baseline Visit during the placebo-controlled period and IMP (eptinezumab) at Week 12 Visit during the open-label period. IMP is administered by intravenous infusion over 30 minutes (with possibility to extend the intravenous infusion by15 minutes).

During the visits with IMP infusion, safety assessments will be performed before and after the infusion. The ePROs must be completed prior to the intravenous infusion. Patients must ensure to complete eDiary recording of headaches prior to the intravenous infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary).

The primary outcome visit is at Week 4 during the placebo-controlled period.

At designated sites, optional actigraphy assessments using a digital device will be performed on a consenting subset of patients. Patients can withdraw from these optional assessments without withdrawing from the main study.

Patients will be scheduled for a Safety Follow-up Contact (at Week 32), 8 weeks after EoS Visit.

Patients who withdraw their consent should be withdrawn from the study. However, all efforts should be done to keep the patients who interrupted/terminated their IMP in the study and all assessments should be performed as described in the protocol. If patients want to withdraw from the study and thus not willing to attend the remaining visits as scheduled, they will be asked to attend a Withdrawal Visit as soon as possible and a Safety Follow-Up Contact, 20 weeks after the last administration of IMP.

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

3.2 Rationale for the Study Design

This study is a placebo-controlled study in patients with a dual diagnosis of migraine and MOH. The sample size for the primary endpoint is chosen based on the phase 3 data with eptinezumab in the sub-population of patients with migraine and MOH, a study that did not include systematic education[36], and on a study of combining preventive therapy chosen according to current guidelines and a withdrawal programme.[9]

The primary endpoint is to evaluate the efficacy of eptinezumab as add-on to BI for the prevention of migraine and treatment of MOH.

Fulfilment of criteria for migraine, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the screening period, that is, migraine occurring on ≥8 days and headache occurring on ≤26 days. The proposed study population comprises patients who have at least 8 migraine days per month. Based on prior studies in migraine, this target population is justified based on a lower heterogeneity of the data and an optimized chance of getting a conclusive result. The rationale for an upper limit on the number of headache days is to exclude patients with chronic daily headaches (for example, hemicrania continua, new daily persistent headache). Prior to randomization, the investigator will review the data in the *eDiary Eligibility Report* to determine if eligibility criteria are fulfilled.

The definition of a migraine day in the protocol is based on the IHS guidelines[1] for controlled studies of preventive treatment of migraine in adults. Patients will be asked, based on daily questions in the eDiary, if they took any medications to treat a headache and, if so, did at least one medication successfully treat the headache. Furthermore, the patients will be asked to register the medication used. The master medication list will be classified into *migraine-specific* and *non-migraine-specific medication* to ensure that a migraine day is classified correctly as a day that is successfully treated with migraine-specific acute medication.

Fulfilment of criteria for MOH based on the investigators interview with the patient according to the ICHD-3 criteria, will be confirmed via prospectively collected information in the eDiary during the screening period, that is, headache occurring on ≥15 days and have regular overuse of one or more drugs that can be taken for acute and/or symptomatic treatment of headache

Secondary endpoints evaluating health-related quality of life, such as MBS, as well as work productivity, are included in the study to evaluate the impact of preventive treatment beyond the reduction in number of MMDs and medication overuse.

A study duration of 12 weeks for the placebo-controlled period is in line with the Guidelines of the IHS for controlled studies of preventive treatment of CM in adults[37] and with the previous completed phase 3 studies that showed a persistence of a robust migraine preventive effect of eptinezumab across 12 weeks with administration every 12 weeks. In addition, treatment of MOH with withdrawal of acute medication is normally evaluated after 8 to 12 weeks in the headache clinics, thus a 12-week study duration for evaluation of the combined effect of BI with eptinezumab for treatment of MOH is justified.

A further 12-week open-label period with eptinezumab treatment is included to provide further relief and gain exploratory data on the durability of a potential remission of the MOH. The open-label part will also ensure all participating patients administered with an active preventive migraine medication and further develop clinical experience with eptinezumab. One dose of eptinezumab (100 mg) is recommended, based on the US FDA and EMA approved labels and the results in the completed phase 3 program, showing similar efficacy on the reduction of MMDs and overall good tolerability of eptinezumab 100 mg and 300 mg in a population of patients with migraine and MOH.

Patients will be randomly allocated to one of two treatment arms of either 100 mg eptinezumab or placebo, with a randomization ratio of 1:1. Inclusion of a placebo group is justified since the group is representative of the best supportive care and there is no current evidence showing that preventive medication and education is better than education alone. Thus, the study will compare the efficacy of eptinezumab and BI *versus* BI alone and no patient will be denied access to acute migraine treatments in this study.

The current study includes the use of digital tools (electronic data collection systems, tele- and phone visits) combined with site visits. Digitalisation and decentralisation of assessments and visits will provide the patient with the possibility of conducting study visits in a remote setting and reduce the burden of attending physical appointments at the clinic. Furthermore, decentralisation will help to ensure a wider representation of trial participants, which is likely to facilitate the recruitment and retention of patients.

The safety assessments will be limited to adverse events and vital signs monitoring including body temperature as this is a phase 4 post-approval study, and the safety and tolerability have been evaluated and established in the extensive clinical programme in the target patient population.

In clinical studies it is not uncommon that events that occur after treatment initiation have the potential to either preclude observation of the study endpoints or affect their interpretation. Such events are termed intercurrent events, and strategies how to address these in order to describe the treatment effect of interest have to be defined. The identified intercurrent events in this study, and the strategies to address them are stated in chapter 2.

4 Ethics

4.1 Ethical Rationale

Eptinezumab 100mg is a recently approved in several countries (including USA, Canada, Australia, and European Union) as a preventive treatment of migraine in adults.

This study will evaluate eptinezumab as a potential treatment candidate add-on to BI for a target patient population with a dual diagnosis of migraine and MOH. Patients will be instructed at Baseline Visit to stop medication overuse during a semi-structured educational conversation.

Inclusion of a placebo group is justified as the group is representative of the best supportive care allowing acute treatment of migraine when prior preventive treatment have not worked. Thus, no patient will be denied access to acute migraine treatment in this study. Furthermore, all patients will receive eptinezumab in the open-label period. No patient will be denied access to active treatment with eptinezumab.

One dose group (100 mg) is considered for the current study as this dose has shown to be efficacious, is generally well tolerated in the treatment of migraine in the phase 3 studies and is approved recommended dose.

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 if considered as necessary by the investigator and/or the patient. However, to comply with the EMA treatment policy strategies, the patient will be encouraged to stay in study for adequate follow up except if she/he withdraws her/his consent.

In accordance with *Good Clinical Practice*,[35] qualified medical personnel at H. Lundbeck A/S 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 Safety Committee at H. Lundbeck A/S to ensure that prompt action is taken, if needed.

In accordance with *Good Clinical Practice*,[35] the investigator will be responsible for all study-related medical decisions.

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.

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 may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

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 8.7)
- of their right to request a copy of their personal data from the study via the investigator
- of their right to be informed by the investigator, after the study has been reported, about which treatment they received
- of their right to receive information about the study results from the investigator on the patients' own initiative; the results will be available approximately 1 year after the end of the study

The patients must be informed that persons authorized by H. Lundbeck A/S and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ECs or 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 ECs or IRBs.

The actigraphy assessments using a digital device is optional, and a *subset-specific Informed Consent Form* is provided for participating in the assessments.

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[38] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of H. Lundbeck A/S, a contractual procedure will be signed between

H. Lundbeck A/S or delegate and the external organization to ensure compliance with the above-mentioned legislation.

4.4 Ethics Committees and Institutional Review Boards

This study will be conducted only after H. Lundbeck A/S 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 H. Lundbeck A/S or the CRO that the required approvals and/or notifications have been received.

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

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

4.5 European Medicines Agency Treatment Policy

The patients are encouraged to stay in the study even if they interrupt/terminate their IMP infusion to allow for EMA treatment policy strategies to be applied. Patients who withdraw the informed consent or who are not compliant with the study procedures should be withdrawn from the study (see section 5.4).

5 Study Population

5.1 Number of Patients and Sites

Planned regions: Approximately 70 sites in select countries across North America, Australia, and Europe.

Planned number of screened patients:	1140
Planned number of randomized patients:	570

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 is an outpatient.
4. The patient has adequate venous access for administration of IMP.
5. The patient has a diagnosis of CM as defined by IHS ICHD-3 guidelines[1] confirmed at the Screening Visit.
6. The patient has a history of migraine onset of at least 12 months prior to the Screening Visit.
7. The patient has ≥8 migraine days per month for each month within the past 3 months prior to the Screening Visit.
8. The patient has a diagnosis of MOH as defined by IHS ICHD-3 guidelines[1] confirmed at the Screening Visit.
9. The patient has ≥15 headache days per month for each month within the past 3 months prior to the Screening Visit.
10. The patient has regular overuse of one or more drugs (section 9.1.1) that can be taken for acute treatment of headache, for >3 months prior to the Screening Visit.
11. The patient has ≥15 to ≤26 headache days, of which ≥8 days were assessed as migraine days during the screening period, based on prospectively collected information in the eDiary.
12. The patient overuses drugs that can be taken for acute treatment of headache during the screening period, based on prospectively collected information in the eDiary.
13. The patient has a history of treatment failure with at least 1 preventive treatment within the last 5 years prior to the Screening Visit due to lack of efficacy (no clinically meaningful improvement at the locally recommended dose for at least 3 months) as defined in section 9.1.1.
14. 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.
15. The patient has had an onset of migraine diagnosis at ≤50 years of age.
16. The patient is aged ≥18 and ≤75 years at the Screening Visit.
17. The patient, if a woman, must:
    - have had her last natural menstruation ≥12 months prior to the Screening Visit and had a high FSH level in the postmenopausal range as per local thresholds to confirm a

postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, OR
- have been surgically sterilized (including tubal ligation, tubal occlusion, and oophorectomy) prior to the Screening Visit, OR
- have had a hysterectomy prior to the Screening Visit, OR
- remain sexually abstinent, when this is in line with her preferred and usual lifestyle, OR
- engage exclusively in same-sex relationships, OR
- agree not to try to become pregnant during the study AND use at least one of the below adequate contraception:
    - combined oral, intravaginal, or transdermal hormonal contraception
    - progestogen-only oral, injectable, or implantable hormonal contraception
    - intrauterine devices
    - intrauterine hormone-releasing system
    - 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 Screening Visit)

18. The patient has provided a signed optional *subset-specific Informed Consent Form* for actigraphy assessments, if applicable.

Exclusion Criteria

1. The patient has previously been enrolled in this study.
2. The patient has experienced failure on a previous preventive treatment targeting the CGRP pathway including gepants for acute or preventive use.
3. The patient has participated in a clinical study <30 days or has taken any investigational products within 5 plasma half-lives (whichever is longer) prior to the Screening Visit.
4. The patient is a member of the study personnel or of their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
5. The patient is pregnant, planning to become pregnant, or breastfeeding.
6. The patient has a history of severe drug allergy or hypersensitivity or known hypersensitivity or intolerance to any of the IMPs or its/their excipients.
7. The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, chronic low back pain, and complex regional pain syndrome).
8. The patient has a diagnosis of acute or active temporomandibular disorders.
9. 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), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura, and migraine with

neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).

10. The patient has psychosis, bipolar mania, dementia, or any other psychiatric conditions whose symptoms are not controlled or who has not been adequately treated for a minimum of 6 months prior to the Screening Visit.
11. The patient has a current diagnosis or history of substance or alcohol use disorder (DSM-5® criteria) <24 months prior to the Screening Visit.
12. 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.
13. 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 CNS functioning.
14. 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.
15. The patient has a history of clinically significant cardiovascular disease including uncontrolled hypertension, vascular ischaemia, or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
16. 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.
17. The patient takes or has taken recent or concomitant medication that is disallowed or allowed with restrictions (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of these medications during the study.
18. The patient has one or more clinically significant out-of-range vital signs at the Screening Visit.
19. The patient has a BMI ≥39 kg/m^2 at the Screening Visit.
20. The patient has tested positive for HIV, anti-HCV, or hepatitis B serology that is confirmed to have acute or chronic infection (Appendix III for interpretation).
21. 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
    - an ALT or AST value >2 times the upper limit of the reference range
22. The patient has, at the Screening Visit, an abnormal ECG that is, in the investigator's opinion, clinically significant.
23. The patient has a QT_{cF} >450 ms (for men) or >470 ms (for women) at the Screening Visit, as calculated by the ECG equipment and evaluated by the investigator. The ECG may be repeated if any of the values are out of range or abnormal.

24. The patient is, at the Screening 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, 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 from the Study and IMP

A patient must be withdrawn from the study if:

- the patient withdraws consent (defined as a patient who takes back consent); section 8.7 states how the patient's data will be handled
- 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])

A patient must be withdrawn from further treatment with IMP if:

- the patient has been randomized in error and has not received IMP
- any site personnel break the randomization code for that patient before the patient has entered in the open-label period
- the investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn from treatment
- the patient experiences an anaphylactic reaction or another serious and/or severe hypersensitivity reaction to the IMP infusion, as assessed by the investigator. If the event occurs during the infusion, the infusion must be discontinued immediately.

Patients who interrupt/terminate their IMP infusion are encouraged to complete the study to allow for application of treatment policy strategies (see section 4.5). Patients who withdraw from treatment with IMP will not be replaced.

6 Investigational Medicinal Product

6.1 Treatment Regimen

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

The patient will receive IMP at the Baseline Visit with either eptinezumab or placebo by intravenous infusion.

At the Visit 5 all patients who were assigned to either eptinezumab or placebo will enter the open-label period and receive an intravenous infusion with eptinezumab 100 mg.

6.2 IMP, Formulation, and Strength

The IMP supplied by H. Lundbeck A/S in this study is:

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

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

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

The pharmacist or designee responsible for receiving, storing, preparing, and dispensing eptinezumab and placebo intravenous 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 minutes (+15 minutes) by the blinded investigator or designee.

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

6.3 Manufacturing, Packaging, Labelling, and Storage of IMP

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 H. Lundbeck A/S.

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

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

No manipulation, repackaging, or relabelling of IMP is permitted after QP release by H. Lundbeck A/S, 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 Medication number.

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

6.4 Method of Assigning Patients to Treatment

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. Randomization of the patient will be performed by using the IRT system and stratified by country and number of previous preventive treatment failures (≤2; >2) occurring up to 5 years prior to Baseline Visit. The IRT will allocate the patient to a treatment group during the call and assign 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 unblinded pharmacist or designee must maintain an adequate record of the receipt and distribution of the IMP(s). This record must be available for inspection by the unblinded CRA at any time.

6.6 Unblinding Procedures

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

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

The investigator may only break the code for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator should consult the CRA (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. 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.

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

Concomitant medication is any medication other than the IMP and that is taken during the study, up until the Safety Follow-up Contact, including during the screening period.

The concomitant medications that are disallowed or allowed with restrictions during the study are summarized in Appendix II. Some of the restrictions apply up until the EoS Visit (Week 24) after which the investigator should continue to treat the patient as required by the patient's clinical condition. The restriction for use of mAb targeting the CGRP pathway must also be applied during the safety follow-up period.

Acute medication for treatment of migraine (triptans, ergotamine, combination of non-opioid analgesics, individual non-opioid analgesics, opioid analgesics, and NSAIDs) is allowed for the entire duration of the study and will be collected in the eCRF and the eDiary. Investigators must ensure the patients are informed to which class of medication(s) their acute treatment(s) belong to.

Details of all concomitant medication (prescription and OTC), traditional herbal medicines, non-pharmacological interventions, and vitamin and mineral supplements for the treatment of migraine taken <3 months prior to the Screening Visit must be recorded in the eCRF at the Screening Visit. Any changes (including reason for changes) in these therapies must be recorded at each subsequent visit.

Details of all migraine preventive medications including treatment failures (prescription and OTC) taken within 5 years prior to the Screening Visit must be recorded in the eCRF at the Screening Visit.

For any concomitant medication, traditional herbal medicines, non-pharmacological interventions, and vitamin and mineral supplements 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 of these therapies initiated due to a new disorder after enrolment in the study, the disorder must be recorded as an adverse event.

7.1 Interaction with Coronavirus Disease 2019 Vaccine

There is currently no data indicating that eptinezumab may interact with or impair the body's immunological response to the COVID-19 vaccines. Hence, there are no indications for safety concerns of concomitant use of the COVID-19 vaccines with eptinezumab. As such, COVID-19 vaccination is allowed during the eptinezumab studies with the guidance measures as described in Appendix II. All adverse events, including those judged by the investigator to be related to the COVID-19 vaccine, must be recorded on an *Adverse Event Form*. A causality assessment, including an alternative causality as relevant, must be provided on the *Adverse Event Form*.

8 Study Visit Plan

8.1 Overview

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

The Screening Visit (Visit 1) is performed 28 to 30 days before the Baseline Visit (Visit 2). Thereafter, study visits during the placebo-controlled period consist of two decentralized contacts (Visit 3 and Visit 4) including the Primary Outcome Visit at Visit 3. During the open-label period, IMP will be administered at Visit 5 followed by a decentralized contact (Visit 6) and an EoS Visit (Visit 7).

IMP will be administered at the Baseline Visit (Visit 2) and Week 12 Visit (Visit 5) which is performed 12 weeks after the Baseline Visit.

The EoS Visit (Visit 7) will be performed at Week 24, 12 weeks after the second IMP administration. A Safety Follow-up Contact (Visit 8) will be performed 8 weeks after the EoS Visit. Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible and a Safety Follow-Up Contact at 20 weeks after last administration of IMP.

At the on-site visits all assessments may be completed over a maximum of 2 consecutive days (with the exception of ePROs); if so, the first day is considered the "visit" day according to the schedule. If the date of an on-site visit or decentralized contact does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit.

Patients will record headache data daily in eDiary from the Screening Visit until the EoS/Withdrawal Visit. Throughout the double-blind and open-label periods compliance check of eDiary data will be conducted at each on-site visit and decentralized contact.

ePROs scheduled at Baseline Visit (Visit 2) and Week 12 Visit (Visit 5) must be completed in the clinical site at the visit date and before the infusion. ePROs which are scheduled in alignment with the Withdrawal Visit can be completed in the clinical site or in the remote setting within 3 days prior to the scheduled on-site visit date. ePROs which are scheduled in alignment with a decentralized contact must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled decentralized 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)

The Screening Visit must be conducted as an on-site visit. Signed informed consent must be in place before any study-related assessments are performed and may be obtained prior to the Screening Visit. Further details on screening assessments are provided in section 9.1.

At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary and ePROs (efficacy and pharmacoeconomic assessments). Details will be provided in a separate *eDiary and ePRO Training Module*. Further details on eDiary are provided in section 9.2.1.2.

In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended by an extra period of seven days with approval from the sponsor provided the medical expert at H. Lundbeck A/S (or the CRO's medical monitor) accepts the rationale provided for the extension.

Prior to the Baseline Visit, study-specific eligibility must be reviewed by the CRO's medical monitor before randomization, to advise if the patient appears eligible according to the selection criteria of the protocol.

8.2.1 Pre-screening

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

8.2.2 Patient Identification Card

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

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

8.2.3 Re-screening

Re-screening is not allowed in this study.

8.3 Baseline Visit + IMP (Visit 2)

The Baseline Visit must be conducted as an on-site visit and will occur 28 to 30 days after the Screening Visit. In exceptional cases, the screening period (visit interval between Screening and Baseline Visits) may be extended with approval from the sponsor provided the medical expert at H. Lundbeck A/S accepts the rationale provided for the extension.

Prior to the Baseline Visit, study-specific eligibility must be reviewed by the CRO's medical monitor before randomization, to advise if the patient appears eligible or not according to the selection criteria of the protocol.

At the Baseline Visit, inclusion and exclusion criteria review must be done prior to dosing (see section 5.3 for further details on selection criteria). A compliance check of eDiary, based on the 28-day screening period, will be conducted and the patient must be assisted with re-training if necessary.

On the Baseline Visit day, patients must ensure to complete eDiary recording of headaches that ended prior to infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary). Further details on eDiary are provided in section 9.2.1.2.

ePROs which are scheduled in alignment with the Baseline Visit must be completed in the clinical site. The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is preferable that the same order of assessments is used per patient and the scheduled time of the day for the assessments is as consistent as possible across all the study visits. Further details on ePROs are provided in sections 9.2 and 9.3.

At the Baseline Visit the patients will receive a dose of IMP. Further instructions on procedures associated with administering the IMP are provided in section 6.2 and *Infusion Guidelines*.

Before IMP infusion:

- Patients must complete the ePROs. ePROs can be completed at the patient's convenience before the pre-infusion blood and urine sampling.
- The following assessments must be conducted: vital signs including body temperature, concomitant medications, adverse events, substance use, urine sampling for pregnancy test, and optional digital device assessment (for patients on a consenting subset). Vital signs must be assessed prior to blood sampling.
- On the Baseline Visit day, patients will follow semi-structured interview based on BI including SDS:H which must take place prior to IMP infusion.

During IMP infusion:

- Patients must be monitored during the infusion in accordance with usual clinical practice. Adverse events, including IRRs, must be checked during the infusion.

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

- Patients must be monitored according to usual clinical practice.
- The following assessments must be conducted: vital signs including body temperature, and adverse events, including IRRs.
- Patients will be requested to stay for as long as the investigator or designee determine this is clinically warranted. After the infusion, the patients will be under observation, but not

confined to bed, unless the investigator or designee decides, based on the patient's condition, that it is in the best interest of the patient to be confined to bed.

8.4 Decentralized Contacts (Visits 3, 4, and 6)

Decentralized contacts will be conducted as telephone or telemedicine visits for an eDiary compliance check, to ensure that selected ePROs have been completed (Visit 3) and for collection of relevant information such as adverse events and concomitant medication (Visits 3, 4, and 6) and substance use (Visits 3 and 4). Decentralized contacts should be planned to maintain the visit schedule relative to the Baseline Visit.

At Visits 3, 4, and 6, a review and compliance check of eDiary data will be conducted and the patient must be assisted with re-training if necessary. Further details on eDiary are provided in section 9.2.1.2

Additionally, at Visit 3, ePROs assessment which are scheduled in alignment with a decentralized contact must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled contact date. The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is preferable that the same order of assessments is used per patient and the scheduled time of the day for the assessments is as consistent as possible across all the study visits. Further details on ePROs are provided in sections 9.2 and 9.3.

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

8.5 Week 12 Visit + IMP (Visit 5)

The Week 12 Visit must be conducted as an on-site visit and should be planned to maintain the visit schedule relative to the Baseline Visit.

Patients will receive an IMP infusion with eptinezumab 100 mg at Week 12 Visit.

Before IMP infusion:

- Patients must complete the ePROs. ePROs can be completed at the patient's convenience before the pre-infusion blood and urine sampling.
- The following assessments must be conducted: vital signs including body temperature, concomitant medications, adverse events, substance use, urine sampling for pregnancy test, and optional digital device (actigraphy) assessment (for patients on a consenting subset).
- On the Week 12 Visit day, the SDS:H must take place prior to IMP infusion.

During IMP infusion:

- Patients must be monitored during the infusion in accordance with usual clinical practice. Adverse events, including IRRs, must be checked during the infusion.

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

- Patients must be monitored according to usual clinical practice.
- The following assessments must be conducted: vital signs including body temperature, IRRs, and adverse events including IRRs.
- Patients will be requested to stay for as long as the investigator or designee determine this is clinically warranted. After the infusion, the patients will be under observation, but not confined to bed, unless the investigator or designee decides, based on the patient's condition, that it is in the best interest of the patient to be confined to bed.

A compliance check of eDiary will be conducted. Patients will be reminded to continue the daily eDiary assessments until the EoS/Withdrawal Visit. Details will be provided in a separate *eDiary and ePRO Training Module*. Further details on eDiary are provided in section 9.2.1.2.

Patients undergoing the optional digital device (actigraphy) assessments will hand in the device, or who withdraw from the study before the Week 12 Visit must hand in the device at the Withdrawal Visit.

ePROs which are scheduled in alignment with the Week 12 Visit must be completed in the clinical site on the visit date and prior to infusion. The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is 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. Further details on ePROs are provided in sections 9.2 and 9.3.

8.6 End of Study Visit (Visit 7)

The EoS Visit (Visit 7) must be conducted as an on-site visit and is performed 12 weeks after the Week 12 Visit. The EoS Visit should be planned to maintain the visit schedule relative to the Baseline Visit.

At the EoS Visit assessments of safety and information collection of concomitant medication will be performed.

A compliance check of eDiary will be conducted. The eDiary closeout will take place at the EoS Visit or Withdrawal Visit (for patients who withdraw from the study prior to the EoS Visit) while the patient is at the site. Details will be provided in a separate *eDiary and ePRO Training Module*. Further details on eDiary are provided in section 9.2.1.2.

ePROs which are scheduled in alignment with the EoS Visit can be completed either in the clinical site or in the remote setting within 3 days prior to the scheduled on-site visit date. The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is 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. Further details on ePROs are provided in sections 9.2 and 9.3.

8.7 Withdrawal Visit

Interruption/termination of IMP infusion does not imply that the patient will be withdrawn from study (refer to section 5.4 for further details). The patient should be withdrawn from the study only if he/she withdrew the informed consent or not compliant with study procedures. All efforts should be done to keep the patient in the study until the end of the study period and all assessments should be done as specified in the protocol.

Patients who withdraw from the study will be asked to attend a Withdrawal Visit. The visit must be scheduled as soon as possible after withdrawal, and further a Safety Follow-Up Contact at 20 weeks after last administration of IMP (except for the patient who withdraw the inform consent).

The eDiary closeout will take place at the Withdrawal Visit (for patients who withdraw from the study prior to the EoS Visit) while the patient is at the site. Details will be provided in a separate *eDiary and ePRO Training Module*. Further details on eDiary are provided in section 9.2.1.2.

If the patient withdraws during the placebo-controlled period, substance use will also be collected. If the patient withdraws from the study, ePROs should also be completed.

ePROs which are scheduled in alignment with the Withdrawal Visit can be completed either in the clinical site or in the remote setting within 3 days prior to the scheduled on-site visit date. The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is 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. Further details on ePROs are provided in sections 9.2 and 9.3.

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 10.6).

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 decentralized contact, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including that visit will be used.

  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical records.
- if the patient explicitly requests that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected.

8.8 Safety Follow-up Contact (Visit 8)

The Safety Follow-up Contact will be conducted as a telephone or telemedicine visit 8 weeks after the EoS Visit (20 weeks after the last administration of IMP).

A safety follow-up is conducted to capture adverse events that occur during the safety follow-up period as well as to follow up on the outcome of adverse events ongoing at the end of the EoS/Withdrawal Visit. For patients who withdraw from the study, except for those who withdraw their consent, the Safety Follow-up Contact should be scheduled after the Withdrawal Visit and 20 weeks after the last administration of IMP.

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

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

8.9 Unscheduled Visits

An unscheduled visit may occur throughout this study if needed. Unscheduled visits can be completed if required as either site visit or decentralized contacts. At these visits, any needed clinical investigations can be performed, and the results can be reported in connection with an adverse event reporting (chapter 10) or documented in the medical records, as applicable.

8.10 End-of-study Definition

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

9 Assessments

9.1 Screening and Baseline Procedures and Assessments

9.1.1 Demographics and Baseline Characteristics

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

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

- demographics (age, sex, and race)
- migraine history (including diagnosis of MOH)
- relevant history (social, medical, psychiatric, neurological)
- previous migraine preventive medication use including treatment failures (see below for definition)* within the 5 years prior to the Screening Visit (see chapter 12 for adequately documented records for migraine and MOH history)
- other recent medication (including migraine medications)
- height and weight without shoes
- examinations (physical and neurological)
- blood sample for eligibility (β-HCG, HIV, anti-HCV, hepatitis B serology) and other clinical safety laboratory tests (as listed in Panel 6)
- urine sample for eligibility (drug screen, alcohol screen) and other clinical safety laboratory tests
- Vital signs (including body temperature) and ECGs
- Signs and symptoms present at screening and/or baseline before IMP administration (recorded on an *Adverse Event Form*)
- Substance use (alcohol, tobacco, caffeine, marijuana consumption) **
- C-SSRS
- optional digital device (actigraphy) assessment

* 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 event) and/or contraindications (that is, ineligibility due to medical reasons).

** Substance use during the screening period will be collected at the Baseline Visit. Substance use throughout the study will be collected at all visits until the Week 12 Visit/Withdrawal Visit (if the patient withdraws during the placebo-controlled period).

9.1.2 Diagnostic Assessments

IHS ICHD-3 guidelines[1] section 1.3 for migraine listed in Panel 4 are the diagnostic criteria to be used by the investigator when assessing patient eligibility.

Panel 4 IHS ICHD-3 Guidelines for Migraine

1.1 Migraine without aura	1.2 Migraine with aura
A. At least five attacks fulfilling criteria B to D B. Headache attacks lasting 4 to 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 to 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.	

For the diagnosis of MOH, the investigator will make the diagnosis by using the IHS ICHD-3 guidelines[1] listed in Panel 5.

Panel 5 IHS ICHD-3 Guidelines for MOH

A. Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache C. Not better accounted for by another ICHD-3 diagnosis Regular overuse is defined either on: • 10 days of use/month for >3 months of ergotamine, triptan, opioid (butalbital in US), or combination of analgesics • 15 days of use/month for >3 months of non-opioid analgesics (paracetamol [acetaminophen], acetylsalicylic acid, NSAIDs)

In order to meet the eligibility with regards to MOH for the study, a patient has to have headache on ≥15 days/month for each month within the past 3 months prior to the Screening Visit and have regular overuse of one or more drugs that can be taken for acute and/or symptomatic treatment of headache, for >3 months.

9.1.3 Classifications for Eligibility

Fulfilment of criteria for migraine, according to the eligibility criteria in this protocol, will be confirmed via prospectively collected information in the eDiary during the screening period, that is, migraine occurring on ≥8 days and headache occurring on ≥15 to ≤26 days. Prior to randomization, the investigator will review the data in the *eDiary Eligibility Report* to determine if eligibility criteria are fulfilled.

Definition of a Migraine Day: The migraine day definition is based on the IHS guidelines[1] for controlled studies of preventive treatment of migraine in adults and here defined as a day with a headache that:

- lasts at least 30 minutes and meets ICHD-3 criteria C and D for migraine without aura (1.1) (following HIS corporate round table meeting held on 17th December 2021, consensus on changing the duration to 30 minutes for both EM and CM)
- or lasts at least 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 (without the condition on 72 hours), C and D for migraine without aura (1.1) (probable migraine**)
- or is a day with a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication (for this purpose the master medication list will be classified into *migraine-specific* and *non-migraine-specific medication*) ***

Data on characteristics of a headache will be collected in the eDiary for each headache, and for each headache it will be determined if it qualifies as a migraine day.

If a headache lasts ≥72 hours, the days will still be counted as *headache days* or *migraine days* as aligned with the IHS guidelines. [1]

A day where the symptoms are not recorded for an ongoing headache (missed data entry) will be classified as a headache day.

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: *"Did you experience an 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). 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 today?*" and "*Did at least one of the medications you took today successfully treat your headache?*?" Only if both are affirmed, and the medication reported by the patient is classified as *migraine-specific*, 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 fulfils the criteria for a migraine, is also referred to as a migraine attack. A migraine attack can last for a single day or for multiple days.

Definition of a Headache Episode: A headache that either lasts ≥30 minutes or qualifies as a migraine, is also referred to as a headache episode. A headache episode can last for a single day or for multiple days.

Definition of an eDiary Compliant Day: A compliant day is defined as any day where the following information is available:

- headache diary is completed: a headache event is reported to take place and the patient has recorded the daily symptoms
- headache diary is completed: confirming that the patient did not have any new headache to report

9.1.4 Urine Drug and Alcohol Screen

A urine drug screen will be performed at the central laboratory at the Screening Visit only. If the patient has tested positive for drugs of abuse (cocaine, amphetamines, phencyclidine, propoxyphene), then the patient should be excluded. Note: positive result for benzodiazepines or cannabinoids is not an exclusion criterion.

9.1.5 Reference Therapy

Reference therapy is BI for MOH, which is a semi-structured educational conversation with the purpose on helping the patients to reduce their MOH. The BI starts with five questions of the SDS:H (including an indication of the patient's willingness and confidence to change his/her medication overuse). Then patient is shown a short-structured scheme bases presentation either on a flip-over or slides with information about MOH and the association between medication overuse and chronic headache. The interview will end with an agreed plan on how to stop or reduce the medication overuse.

The consultation is done in an empathic and collaborative manner aiming at achieving a decision by the patient that he/she would cut down the offending medication. Explicit recommendations are to stop or to reduce headache medications towards safe levels and information about possible difficulties and gains including that MOH usually "gets worse before it improves.

The BI will take approximately 10 minutes to complete and is performed at Baseline Visit before IMP infusion.

The investigators and the study staff will be trained during the investigator meeting on the administration of the BI. A demonstration video on how to conduct the BI will be mandatory training for study personnel involved in submitting this intervention to the study population.

9.2 Efficacy Assessments

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

Patients will record eDiary headache data on daily basis from the time of screening until the EoS/Withdrawal Visit. At each on-site visit and decentralized contact during the placebo-controlled period (that is, every 4 weeks), a compliance check of eDiary will be conducted (based on eDiary reporting). Additionally, ongoing evaluation of eDiary compliance will be performed by the site and more frequent contact with patients may be needed in case of non-compliance. On on-site visit days, patients must complete the daily eDiary entries prior to infusion.

Patients will complete the PGIC, MBS, and HADS along with the pharmacoeconomic assessment ePROs (see section 9.3). The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is 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.

ePROs will be completed in alignment with on-site visits and decentralized contacts:

- *ePROs which are scheduled in alignment with an on-site visit* (see Panel 2): can be completed in the clinical site or in the remote setting within 3 days prior to the scheduled

on-site visit date. On the Baseline Visit day and Week 12 Visit day, patients must complete the ePROs on the visit date and prior to infusion.

- *ePROs which are scheduled in alignment with a decentralized contact* (see Panel 2): must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled decentralized contact date.

9.2.1 Clinical Outcome Assessments

9.2.1.1 Use of eCOA Tools

The eCOA tools are the eDiary and ePROs, and guidance will be given on how to complete them to the patients by designated site staff (see section 9.2.1.8). Detailed instructions will be provided to the site in a separate *eDiary and ePRO Training Module and Site Information Guide*. Site staff will be given access to review the eDiary data.

The eCOA tools will be administered electronically in the local language. Only those provided by H. Lundbeck A/S that have been validated in the language to which they have been translated will be used in this study.

The following eCOA tools will be used for efficacy assessments:

- eDiary – to assess daily headache and migraine variables, that is, the number of hours with headache, presence of associated symptoms, use of acute migraine medications start and stop dates, and 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.
- HADS - to assess psychological distress in non-psychiatric patients.
- SDS:H - to assess dependency-like behaviour in patients with headache.

9.2.1.2 Electronic Diary

At the Screening Visit, the patient must be assisted with the provisioning of the eDiary and must be trained in eDiary use and compliance requirements by designated site staff. Patients will be instructed to complete the eDiary on a daily basis, from the time of screening until the EoS/Withdrawal Visit. During the EoS/Withdrawal Visit, eDiary close-out must be performed while the patient is at the site. Details will be provided in a separate *eDiary and ePRO Training Module*.

The content of the headache eDiary is developed on key symptoms and characteristics as mentioned in the definition of migraine (see sections 9.1.2 and 9.1.3). The eDiary consists of applications and reports which will be used to derive the headache and migraine endpoints, and medication use. For each day, the patient will record if they experienced any headaches. For each experienced headache, the start and stop date and time will be collected. The patient will record further daily information regarding headache characteristics (for instance, headache severity, additional symptoms) and intake of headache/migraine acute medication.

Headache items will be assessed with a yes/no response; and severity will be rated as mild, moderate, or severe. Additional details regarding the questions that patients will answer can be found in the *eDiary and ePRO Training Module*.

The Screening Visit will correspond to the day of eDiary distribution and will start the 28-day eDiary screening period. Any patient found to be ineligible for the study during the screening period will not be randomized. An *eDiary Eligibility Report* will be used to review headache eDiary data (including baseline headache and migraine days and eDiary compliance) during the 28-day screening period for the eligibility assessment of:

- migraine occurring on ≥8 days and headache occurring on ≤26 days.
- compliance by entry of headache data for at least 24 of the 28 days following the Screening Visit.

On the Baseline Visit day and Week 12 Visit day, patients must ensure to complete eDiary recording of headaches that ended prior to infusion (that is, for headaches which are ongoing or not yet recorded in the eDiary).

Site staff will be given access to the eDiary data. Compliance data (based on eDiary reporting) will be made available until the EoS/Withdrawal Visit to site staff for review on a regular basis. At each on-site visit and decentralized contact (that is, every 4 weeks), a compliance check of eDiary will be conducted. Additionally, ongoing evaluation of eDiary compliance will be performed by the site and more frequent contact with patients may be needed in case of non-compliance. All follow-up with patients regarding eDiary compliance should be documented in the source records.

9.2.1.3 Patient Global Impression of Change

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

9.2.1.4 Most Bothersome Symptom

The investigator will verbally obtain the most bothersome symptom associated with the patient's migraines during the Screening Visit. The selected most bothersome symptom will be incorporated in the electronic version of the MBS (ePRO). Patients will be asked to rate the improvement in this symptom from screening on a 7-point scale identical to the scale used for the PGIC. The MBS areas include nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, mood changes, and other. It takes less than 5 minutes to complete the MBS.

9.2.1.5 Hospital Anxiety and Depression Scale

The HADS is a patient-rated scale designed to assess psychological distress in non-psychiatric patients. The HADS consists of two sub-scales: The D-scale measures depression and the A-scale measures anxiety. Each sub-scale contains 7 items, and each item is rated from 0 (absent) to 3 (maximum severity). The score of each sub-scale ranges from 0 to 21 and are analysed separately. It takes approximately 5 to 10 minutes to complete the HADS.

9.2.1.6 Severity of Dependence Scale Adapted for Headache

The SDS:H is a patient reported scale, designed to assess dependency-like behaviour in patients with headache. The SDS:H is performed as a semi-structured interview, where the following questions will be addressed: 1) Do you think your use of headache medication was out of control? 2) Did the prospect of missing a dose make you anxious or worried? 3) Did you worry about your use of your headache medication? 4) Did you wish you could stop? 5) How difficult would you find it to stop or go without your headache medication? Each item is scored on a 4-point scale ranging from 0 (never/almost never, question 1-4, and not difficult, question 5) to 3 (always/nearly always, question 1-4, and impossible, question 5). It takes less than 5 minutes to complete the SDS:H.

9.2.1.7 External eCOA Monitoring Oversight

H. Lundbeck A/S reserves the right to use external quality oversight methods to ensure the eDiary compliance and data quality, as well as ensure accurate completion of eCOAs. For this study, the CRO agreed with H. Lundbeck A/S will conduct the external data monitoring.

9.2.1.8 eCOA Tool Training

eCOA training will be conducted by the CRO as agreed with H. Lundbeck A/S. Site staff will complete their designated training curriculum based on their initial qualification status and assigned role. The training program will also include general eCOA quality assurance and management guidance.

Only site staff who have adequate experience with migraine and who have received adequate training on good standards in completion of the eDiary and ePROs will be authorized to train the patients on completion of eDiary and ePROs in the study. Documentation of training will be provided to site staff for archiving in the investigator TMF. New eDiary and ePRO trainers joining the study must be trained similarly.

9.2.2 Optional Digital Device (Actigraphy) Assessments

Actigraphy is a non-invasive way of monitoring activity and sleep via an actimetry sensor picking up accelerations in three dimensions. Actigraphy is recorded using a wrist-worn device (EmbracePlus; Empatica, Boston, MA, US) which continuously records physiological data using an accelerometer, an electrodermal activity sensor, and a peripheral temperature

sensor. The data is recorded on the internal memory of the wearable wristband and sent to a paired application via Bluetooth (Care App). Data from the application is transferred to a research portal (Care Portal) via Internet connection. A guide with details on how to use the device will be provided to the patient. The actigraphy device is a voluntary option for this study.

The following actigraphy parameters will be derived to capture physical activity and sleep:

- Movement intensity (activity counts): Time in light PA (11-50 a.U.), moderate PA (51-100 a.U.) and intense PA (101-200 a.U.), minutes per 24 hours.
- Rest: Time in rest period: measured as minutes per 24 hours in the rest epoch state (range 0-300: 0=wake epoch; 101=rest epoch; 102=turn and toss epoch; 300=rest interruption epoch).
- Total Sleep Time: corresponding to the total time identified as sleep, per night in minutes.
- Wake After Sleep Onset: corresponding to the amount of time spent awake after the Sleep Onset Latency, in minutes.
- Sleep Efficiency: corresponding to the percentage of time asleep within the time-in-bed period.
- Sleep Onset Latency: corresponding to the time from the start of the time in bed period to the actual sleep onset, computed from the actigraphy data, in minutes.

9.3 Pharmacoeconomic Assessments

Pharmacoeconomic assessments include ePROs (HIT-6, mMIDAS, MSQ v2.1, EQ-5D-5L, HCRU, WPAI:M, and TSQM-9).

Patients will complete these ePROs along with the efficacy assessment ePROs (section 9.2.1). The ePROs should preferably be completed in the following order: HIT-6, mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU. It is 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.

ePROs will be completed in alignment with on-site visits and decentralized contacts:

- *ePROs which are scheduled in alignment with an on-site visit* (see Panel 2): can be completed in the clinical site or in the remote setting within 3 days prior to the scheduled

on-site visit date. On the Baseline Visit day and Week 12 Visit day, patients must complete the ePROs on the visit date and prior to infusion.

- *ePROs which are scheduled in alignment with a decentralized contact* (see Panel 2): must be completed in the remote setting and can be completed on the day or within 3 days prior to the scheduled decentralized contact date.

9.3.1 Clinical Outcome Assessments

9.3.1.1 Use of eCOA Tools

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

The following eCOA tools will be used for pharmacoeconomic assessments:

- HIT-6 - to assess the impact of an occurring headache and its effect on the ability to function normally in daily life
- mMIDAS - to assess the disability related to migraine
- MSQ v2.1 - to assess quality of life related to migraine
- EQ-5D-5L - to assess the overall state of health
- WPAI:M - to assess overall effect of health on productivity at work and daily activities
- TSQM-9 - to assess the patient's satisfaction with the medication (IMP)
- HCRU - to assess migraine-specific health care resource utilization

9.3.1.2 Headache Impact Test

The HIT-6 (v1.0)[39] 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 Disability Assessment, Modified Version

The mMIDAS[40] is a self-reporting questionnaire designed to assess absenteeism (complete disability) and presenteeism (reduced participation) in several domains, including work, school, family, social, and leisure activities. The total number of days with disability is rated on a 4-point scale, from the lower total score that indicates a Little or No Disability; Mild Disability; Moderate Disability to the higher total score that indicates a Severe Disability. It takes approximately 5 to 10 minutes to complete the mMIDAS.

9.3.1.4 Migraine-Specific Quality of Life Questionnaire, Version 2.1

The MSQ v2.1[41] 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 to 10 minutes to complete the MSQ v2.1.

9.3.1.5 Euroqol 5 Dimension – 5 Levels

The EQ-5D-5L[42] is a patient-reported assessment designed to measure the patient's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a VAS of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS ranges from 0 (*worst imaginable health state*) to 100 (*best imaginable health state*). It takes approximately 5 minutes to complete the EQ-5D-5L.

9.3.1.6 Health Care Resource Utilization

Migraine-specific health care resource utilization information will be collected in terms of outpatient health care professional visits, emergency room visits, hospital admissions, as well as duration of hospital stays. Clinical site personnel and patients will be instructed to capture utilization that takes place outside of visits associated with their participation in the clinical study. It takes approximately 5 minutes to complete the HCRU.

9.3.1.7 Work Productivity and Activity Impairment: Migraine

The WPAI[43] 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: 1 item assess employment status, 3 items assess the number of hours worked, the number of hours missed from work due to the patient's condition, or due to other reasons, and 2 visual numerical scales to assess how much the patient's condition affects their productivity at work and their ability to complete normal daily activities. It takes approximately 5 minutes to complete the WPAI.

9.3.1.8 Treatment Satisfaction Questionnaire for Medicine – 9 Items

The TSQM-9 is a generic questionnaire assessing the patient's satisfaction with the medication (IMP). The tool consists of 9 items addressing effectiveness, side effects, convenience, and overall satisfaction of the IMP. It takes approximately 5 minutes to complete the TSQM-9.

9.3.1.9 External eCOA Monitoring Oversight

Refer to section 9.2.1.7 for further information.

9.3.1.10 eCOA Tool Training

Refer to section 9.2.1.8 for further information.

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 vital signs, 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 6.

Panel 6 Clinical Safety Laboratory Tests

Haematology	**Liver**[b]	**Serology**
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] consent is required S-HBsAg [HBSAG] S-anti-HBs [HBSAB] S-anti-HBc [HBCAB] S-anti-HCV [HCAB]
		Infection S-C-reactive protein [CRP]
Electrolytes[b]	**Kidney**[b]	**Urine**[f]
S-sodium [SODIUM] S-potassium [K] S-calcium (total) [CA]	S-creatinine [CREAT] S-urea nitrogen [UREAN]	U-protein (dipstick) [PROT] U-glucose (dipstick) [GLUC] U-blood (dipstick) [OCCBLD] Urine drug screen Urine alcohol
Endocrine and Metabolic[b]	**Lipids**[b,c]	**Pregnancy**[d]
S-albumin [ALB] S-glucose[d] [GLUC] B-HbA1c [HBA1C] S-creatine phosphokinase [CK] S-thyroid-stimulating hormone[c] [TSH][g] S-follicle-stimulating hormone [FSH][e]	S-low density lipoprotein [LDL] S-high density lipoprotein [HDL] S-triglycerides [TRIG] S-cholesterol (total) [CHOL]	S-human chorionic gonadotropin [β-HCG] Urine dipstick
B = blood; P = plasma; S = serum; U = urine; [ ] = CDISC term		

a Count and % of total leucocytes

b Clinical chemistry

c Fasting, when possible

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

e Only for women

f If urine dipstick is positive, a urine microscopic panel will be conducted.

g In case of abnormal TSH, reflex testing of T3 and T4 will be conducted.

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. In case of exceptional circumstances or emergency, the investigator may need to request additional laboratory testing at a local laboratory. The investigator will record only out-of-range clinical safety laboratory test values considered clinically significant, which must be recorded as an adverse event on an *Adverse Event Form*.

Urine pregnancy testing will be performed and analysed at site. All other urine samples will be collected and 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). 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 Including Body Temperature

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

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

Vital signs including blood pressure, pulse, respiratory rate and body temperature must be assessed prior to blood sampling.

Respiratory rate will be measured by counting the number of breaths over a full minute.

Body temperature will be measured by a thermometer that is used at the site.

Any out-of-range vital signs 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 without shoes 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

All ECG apparatus must be calibrated, meaning that an electrical impulse of a given strength always results in a wave of a given height. Standard calibration is 10 mm/mV. This means that an electrical impulse of 1 mV results in a wave height of 10 mm on the ECG. A calibration test must be present on the ECG hardcopy.

The ECG recording should be a 12-lead recording. All leads should be clearly identified. There should be 3 evaluable beats per lead.

Paper speed (preferably 25 mm/sec) should be stated on the ECG. The relevant following information should also be stated on the ECG recording: Study number, patient's name and date of birth, and date and time of recording. The person (investigator or its designee) who interprets the ECG should preferably sign and date the ECG after it has been reviewed.

Upon request from the investigator, a standard 12-lead ECG will be provided to the investigator or its designee.

The results of ECG will include the RR, PR, QRS, QT, and QTc intervals.

If the ECG is out of the reference range, it is the investigator's responsibility to assess the value as "Normal," "Abnormal Not Clinically Significant," or "Abnormal Clinical Significant" and handle it in the appropriate manner. 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* and must be described in words with a diagnosis or value (for example, Second-degree AV-Block type Wenckebach) in the eCRF.

9.4.6 Physical and Neurological Examinations

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 and neurological 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 a designee.

If *genito-urinary system evaluation* is not clinically indicated based on patient medical history or symptoms, it is accepted by Lundbeck not to conduct such evaluation. Examination of renal regions are to be included as part of abdominal examination.

The neurological examination must be performed by a physician. The neurological examination must cover the following areas: mental status, examination of all cranial nerves, the motor system, reflexes, the sensory system, and the cerebellar functions.

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.[44] The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of ideation, and 4 questions addressing suicidal behaviour. For this study, the following versions of the scale are used: the "Baseline/Screening" version (lifetime and 1 year assessment). It takes approximately 5 to 15 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 medical doctor, research nurse, psychologist, site/study coordinators, or health care with 2 years of clinical experience and administration of semi-structured interview. Any exceptions must be discussed and approved by H. Lundbeck A/S and/or its designee. 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 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*.

9.5 Order of Assessments

No study-related activities must be conducted until after the applicable *Informed Consent Form* is signed.

At the Screening Visit:

- Blood and urine sampling for clinical safety laboratory tests and ECG recording must be scheduled and results reviewed prior to the Baseline Visit.
- At the Screening Visit the "Baseline/Screening" version of the C-SSRS must be used.

ePROs:

- ePROs scheduled in alignment with an on-site visit without IMP infusion (see Panel 2) can be completed at the clinical site or in the remote setting within 3 days prior to the scheduled on-site visit date. On the Baseline Visit day and Week 12 Visit day, patients must complete the ePROs on the visit date and prior to infusion.
- ePROs which scheduled in alignment with a decentralized contact (see Panel 2) 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
- HIT-6 should preferably be the first ePRO completed, followed by mMIDAS, PGIC, MBS, MSQ v2.1, HADS, EQ-5D-5L, WPAI:M, TSQM-9, and HCRU.
- It is 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.

At the Baseline and Week 12 Visits **prior** to infusion:

- Patients must complete recording of headaches that ended prior to infusion (that is, events not yet recorded in the headache eDiary or events ongoing).
- Patients must complete the ePROs. ePROs can be completed at the patient's convenience before the pre-infusion sampling.
- The following assessments must be conducted: vital signs including body temperature, concomitant medications, adverse events, urine sampling (for pregnancy tests), optional digital device (actigraphy) assessment (for patients on a consenting subset), and BI including SDS:H. Vital signs must be assessed prior to blood sampling at Baseline Visit.
- See sections 8.3 and 8.5 for procedures preceding IMP administration.

At the Baseline and Week 12 Visits **during** infusion:

- Adverse events, including IRRs, must be checked during the infusion.

At the Baseline and Week 12 Visits **after** end-of-IMP-infusion and before the patient is discharged from the site:

- The following assessments must be conducted: vital signs including body temperature and adverse events, including IRRs.
- See sections 8.3 and 8.5 for procedures following IMP administration.

9.6 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 19.2 mL during the study.

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

9.7 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[45]

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 H. Lundbeck A/S 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.

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.

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*[23]) and related to a medicinal product by either the investigator or H. Lundbeck A/S.

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 Management of Reactions to Study Drug

There are no specific antidotes to an infusion of eptinezumab.

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

Should a medical condition arise that the investigator believes is related to the study drug, clinical judgement should be used to provide 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.

Per investigator judgement, it can be considered to collect additional immune response samples in accordance with local clinical practice, such as histamine, tryptase, immunoglobulin E, and complement components C3 and C4.

10.3 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 H. Lundbeck A/S 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.

10.4 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 *Adverse Event 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 H. Lundbeck A/S immediately (within 24 hours) after becoming aware of it (see section 10.5).

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

10.5 Reporting Serious Adverse Events

The investigator must report SAEs to H. Lundbeck A/S 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

H. Lundbeck A/S 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.

H. Lundbeck A/S 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*[46] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, H. Lundbeck A/S will also assume responsibility for reporting SUSARs to the ECs.

H. Lundbeck A/S will assess the expectedness of SAEs and inform the investigators about SUSARs in the blinded SUSAR listings.

10.6 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 Withdrawal visit/Safety Follow-up Contact, whichever comes first. At the Withdrawal visit/Safety Follow-up Contact, information on new adverse events, if any, and stop dates for previously reported adverse events must be recorded.

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

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

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms

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

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

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data will be reviewed and evaluated for accuracy by 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 H. Lundbeck A/S.

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

- Safety laboratory test data
- eDiary data
- Actigraphy
- ePRO data
  - HIT-6

- mMIDAS
- PGIC
- MBS
- MSQ v2.1
- EQ-5D-5L
- HCRU
- WPAI:M
- HADS
- TSQM-9
- SDS:H

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. H. Lundbeck A/S 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 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 should demonstrate due diligence in trying to obtain migraine and MOH history, general medical history, recent medication, previous migraine preventive medication use including treatment failures (within 5 years prior to the Screening Visit).

Acceptable adequately documented records of previous migraine preventive medication use (including treatment failures) are as follows.

- Medical record that includes migraine history and the name of the medications used to treat migraine and if available treatment stop and start dates including dose levels, including treatment failures on preventive treatment for migraine. 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 treating physician, OR
- If the investigator is not the treating physician and medical records cannot be obtained via the treating physician, the investigator should document the lack of availability and confirm medical history
  - via electronic records (for example prescriptions or pharmacy purchase listing when available for shorter term periods) and/or
  - via patient interview

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.

It must be possible to verify all other data in the eCRFs against source documents in the patient's medical records, or in the location stated in the source data agreement.

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 H. Lundbeck A/S, 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

H. Lundbeck A/S 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

H. Lundbeck A/S 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 at the CRO with the agreement with Biostatistics, H. Lundbeck A/S, will perform the statistical analyses described below.

16.2 Analysis Sets

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

- APRS - all randomized patients
- APTS - all patients in the APRS who received an infusion of the IMP in the placebo-controlled period
- FAS - all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline 4-week assessment of MMDs in Weeks 1-12
- APTS-OL - all patients in the APRS who received an infusion of the IMP in the open-label period

The FAS will be used for all efficacy analyses in the placebo-controlled period, and the APTS will be used for all safety analyses in the placebo-controlled period, while the APTS-OL will be used for the safety and efficacy analysis of the open-label period.

After all patients have completed the study, all data will be cleaned and the database will be locked when there are no more patients in the study. The patients and data will be classified into the analysis sets (APRS, APTS, FAS, and APTS-OL) according to these definitions at a *Classification Meeting* held after the database has been released but before unblinding of the study. Next, data will be unblinded for the reporting team, and all analyses specified in the *Statistical Analysis Plan* (SAP) will be performed and included in the *Clinical Study Report*.

16.3 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables and counts and, if relevant, percentages will be presented for categorical variables.

16.4 Patient Disposition

Patient disposition will be summarized by treatment group and include the number of patients in the APTS who completed or withdrew from the study for each period, as well as the number of patients in each analysis set. Note that withdrawal from treatment is not possible for the APTS patients, as they only receive the treatment on one occasion during the

placebo-controlled period. Withdrawal from study after IMP has been infused leads to missing data and the handling of these will be described in the SAP (see also section 16.8.1).

The number of patients who withdrew from the study will be summarized by treatment group and primary reason for withdrawal as well as by treatment group and all reasons for withdrawal.

The summary of patient disposition will be presented for each country and overall.

16.5 Demographics and Baseline Characteristics

Demographics (age, sex, and race), baseline characteristics (height, weight, and BMI), and other disease characteristics will be summarized by treatment group for the APTS. Baseline efficacy variables will be summarised by treatment group for the FAS.

The summary of demographics, baseline characteristics, and other disease characteristics will be presented for each country and overall.

16.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarized by Anatomical Therapeutic Chemical code and generic drug name by treatment group.

Prior and concomitant use of preventive migraine medication will be summarized by treatment group. If relevant, medication overuse status at the screening visit will be provided.

16.7 Exposure

All patients in the APTS are expected to receive one single infusion of the IMP in the placebo-controlled period and one infusion of the IMP in the open-label period. The duration of infusion will be summarized by treatment group and period. Randomized patients whose infusion took more than 45 minutes and patients who had their infusion interrupted will be listed by treatment group, infusion start date/time and end date/time, infusion related reactions, and reasons if any.

16.8 Efficacy Analyses

16.8.1 General Efficacy Analysis Methodology

All the statistical tests of the efficacy endpoints will be two-sided tests performed at the 5% significance level and all CIs will be 95% CIs, unless otherwise specified.

Efficacy analyses will be based on FAS.

A detailed plan for the selection of values for each patient, as well as the handling of missing data and intercurrent events, in alignment with the estimands specified under chapter 2, will be described in the SAP.

16.8.2 Primary Analysis of the Primary Endpoint

The main estimator for the primary estimand is defined as the estimated effect from the MMRM.

The number of MMDs will be summarized by daily eDiary data across Weeks 1 to 4, Weeks 5 to 8, and Weeks 9 to 12. Details on derivation and imputations of days with missing or incomplete eDiary data will be described in the SAP.

The primary endpoint, change from baseline in the number of MMDs, will be analysed using MMRM with the number of MMDs at baseline as a continuous covariate and including treatment group (eptinezumab *versus* placebo), month (Month 1: Weeks 1 to 4; Month 2: Weeks 5 to 8; Month 3: Weeks 9 to 12), country, and previous treatment failures (≤2; >2), as categorical variables. An interaction term between month and treatment as well as between month and number of MMDs at baseline will be included. The model will assume an unstructured covariance matrix to model the within patient variance. The statistical test will be based on the treatment contrast for change from baseline in MMDs (Weeks 1-4).

16.8.3 Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses of the primary endpoint will be described in the SAP.

The primary analysis model will be applied, including an adjustment for whether or not a patient had a COVID-19 vaccination during the 4 weeks following IMP administration.

16.8.4 Analysis of the Key Secondary Endpoints

Estimands for the key secondary endpoints will be described in the SAP. The main estimator for each of the key secondary estimands is defined as the estimated effect from the analysis models described below.

Change from Baseline in MMDs (Weeks 1-12)

The endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the estimated mean MMDs, which is averaged over Weeks 1 to 4 (Month 1), Weeks 5 to 8 (Month 2), and Weeks 9 to 12 (Month 3).

Not Fulfilling the ICHD-3 Diagnostic Criteria for CM nor MOH (Week 4)

The ICHD-3 diagnostic criteria for CM and/or MOH will be checked during Weeks 1 to 4 (as described in the ICHD-3 diagnostic criteria defined respectively in Panel 4 and Panel 5;

further details will be described in the SAP). A response of Yes, if not fulfilling CM and MOH, and No otherwise. The treatment effect will be tested by a 2×2 table using Cochran-Mantel-Haenszel including previous treatment failures as a stratification variable.

Not Fulfilling the ICHD-3 Diagnostic Criteria for CM nor MOH (Week 12)

The endpoint will use the same method as that described for Weeks 1 to 4, except that the ICHD-3 diagnostic criteria for CM and/or MOH will be checked during Weeks 1 to 12.

Change from Baseline in MHDs (Weeks 1-4)

The endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the number of MHDs.

Change from Baseline MHDs (Weeks 1-12)

The endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the estimated mean MHDs, which is averaged over Weeks 1 to 4 (month 1), Weeks 5 to 8 (month 2), and Weeks 9 to 12 (month 3).

Change from Baseline in Average Daily Pain Assessment Score (Weeks 1-2)

The average daily pain will be calculated using the daily pain assessment collected during Weeks 1-2. Change from baseline in average Daily Pain will be analysed using ANCOVA with the average Daily Pain at baseline as a covariate and including treatment group, country, and previous treatment failures, as categorical variables.

Change from Baseline in Monthly Days with Acute Medication Use (Weeks 1-4)

The endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the number of monthly days with acute medication use during Weeks 1-4.

Change from Baseline in Average Monthly Days with Acute Medication Use (Weeks 1-12)

The endpoint will be analysed using the same methodology as that described for the primary analysis, except that the test will be based on the estimated mean monthly days with acute medication use, which is averaged over Weeks 1 to 4 (Month 1), Weeks 5 to 8 (Month 2), and Weeks 9 to 12 (Month 3). All the medication collected in eDiary as acute medication taken to stop headache/migraine attack will be accounted for in the analysis.

16.8.5 Sensitivity Analyses of the Key Secondary Endpoints

Sensitivity analyses of the key secondary endpoints will be described in the SAP.

16.8.6 Testing Strategy

For the primary endpoint (change from baseline in MMDs [Weeks 1-4]), test the hypothesis of no difference between the eptinezumab and placebo using a two-sided test on 5% significance level. If rejected and if the test shows a numerical advantage to eptinezumab, then continue to the first key secondary endpoint (change from baseline in MMDs [Weeks 1-12]).

On the first key secondary endpoint, test the hypothesis of no difference between the eptinezumab and placebo groups. If rejected and if the test shows a numerical advantage to eptinezumab, then continue to the second key secondary endpoint (change from baseline in MHDs [Weeks 1-4]). This continues through the list of key secondary endpoints (change from baseline in MHD [Weeks 1-12], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Week 4], not fulfilling the ICHD-3 diagnostic criteria for CM nor MOH [Week 12], change from baseline in average Daily Pain assessment score [Weeks 1-2], change from baseline in monthly days with acute medication use [Weeks 1-4], change from baseline in monthly days with acute medication use [Weeks 1-12]), until an endpoint fails to reach significance.

16.8.7 Analysis of the Secondary Endpoints

The binary secondary endpoints will be analysed using Cochran-Mantel-Haenszel test including previous treatment failures as stratification variables.

All continuous secondary endpoints addressing changes from baseline to Weeks 1 to 4. Weeks 1 to 12, or Weeks 12 to 24 will be analysed using the same methodology as that described for the primary analysis.

50% Response in MMDs (Weeks 1-4): Defined as a 50% reduction in the average MMDs across the available data from Weeks 1 to 4, will compare eptinezumab *versus* placebo. A logistic regression model will be used, with treatment group as a factor, baseline MMDs as a continuous covariate, and previous treatment failures as a binary covariate. Similar analysis will be done for Weeks 1 to 12. The analyses on 75% response in MMDs during Weeks 1 to 4 and Weeks 1 to 12 will be performed as well. Similar response analyses will be performed for MHDs.

For other secondary efficacy endpoints based on response rates, treatment effects of eptinezumab compared to placebo will be analysed using a logistic regression model, similar to the model defined above.

Health-related quality of life scores test between eptinezumab and placebo at Week 4, Week 12, or Week 24 will use the similar ANCOVA model defined in the analysis of key secondary endpoints.

16.8.8 Analysis of the Exploratory Endpoints

The analysis of the exploratory endpoints will be described in the SAP.

16.8.9 Analysis of Subgroups

The analysis specified for the primary and the key secondary endpoints will be repeated for each region (North America and Europe), excluding the region factor, if there are sufficient data collected from the region.

No hypothesis testing will be conducted in the subgroup analysis. Only the treatment differences relative to placebo and their associated 95% CIs will be estimated and displayed using a forest plot.

Other 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 of first dose of IMP
- *treatment-emergent adverse event* – an adverse event that starts or increases in intensity on or after the date of first dose of IMP

Adverse events, sorted by system organ class and preferred term, will be summarized by treatment group.

Allocation of Treatment-Emergent Adverse Events to Study Periods

Treatment-emergent adverse events may be allocated to study periods (these will be defined in the SAP).

16.9.2 Analysis of Other Safety Endpoints

The vital signs will be summarized by treatment group and period. Potentially clinically significant values will be flagged and summarized.

16.10 Handling of Missing Data

eDiary

Patients who do not complete the eDiary daily will have missing data. It is expected that most missing eDiary data will be sporadic.

For each 28-day period, missing data from the eDiary will be imputed in the following way:

- If the number of days with observations, n, is ≥14 days, the MMDs for the 28-day interval will be calculated as the number of migraine days observed/n×28 (prorated) and rounded off to 2 decimals.
- If n <14, the MMDs for the period will be set to missing.

Further details on derivation and imputations of days with missing or incomplete eDiary data will be described in the SAP.

Quality of Life Questionnaires

For those questionnaires, missing items will not be imputed. However, strategies will be provided separately in the SAP for calculating sub-score or total score with missing individual scores.

Digital Device Data

No imputation will be taken for missing data in the wearable digital device during the study period.

16.11 Interim Analyses

No interim analysis is planned.

16.12 Sample Size and Power

It is assumed that the treatment effect of eptinezumab 100 mg compared to placebo in change from baseline in MMDs (Weeks 1 to 4) will be -1.5 MMDs. The difference between eptinezumab 100 mg and placebo was -2.0 in Study 011, a study that did not include education on MOH, after 4 weeks and –3.1 in the subgroup of patients with CM and MOH. The difference between withdrawal from treatment with and without preventive treatment was –1.7 and –1.4 days after 2 and 4 months.[47]

The SD is assumed to be 6.2, based on the averaged SD across treatment groups in the MOH subgroup of Study 011 on the change from baseline in MMDs (Weeks 1 to 4).

Based on the assumed effect size and SD, using a two-sided test on the 5% significance level, 270 patients per treatment group will provide 80% power for showing an effect on the primary endpoint. Assuming that 5% of patients will not contribute data to the analysis, 285 patients randomized per treatment group or 570 patients randomized in total will be needed.

Sample size re-assessment will be conducted on blinded data when approximately 70% of the patients have been randomized. The SD is estimated in the same model as for the primary endpoint, except that all terms including treatment (main effect of treatment group and

interaction between treatment group and month) are excluded. Based on this estimate, the sample size may be increased, but not decreased.

16.13 Statistical Analysis Plan

An SAP describing the handling of data issues and the planned statistical analyses in more detail will be prepared by Biostatistics at the CRO 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 H. Lundbeck A/S.

17.2 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by the CRO agreed with H. Lundbeck A/S.

17.3 Summary of Clinical Study Results

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

17.4 Publications

The results of this study will be submitted for publication.

H. Lundbeck A/S 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 ICMJE.[48]

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 H. Lundbeck A/S 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 of add-on eptinezumab treatment to brief educational intervention for the preventive treatment of migraine in patients with dual diagnosis of migraine and medication overuse headache
Study No.:	20007A (RESOLUTION)
Edition No.:	1.0
Date of edition:	22 December 2021

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

Authentication

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

International study manager:	PPD
Study Lead/Clinical research scientist:	PPD
Head of Biostatistics:	PPD
Head of Medical Safety:	PPD

Authorization

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

Therapeutic Area Lead:	PPD

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 antimigraine agents. Other medication in the same class is allowed if prescribed for non-migraine indications.
Antihypertensives	See restrictions in use under antimigraine 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 and expected to be maintained until the EoS Visit (Week 24).
Antimigraine agents	Allowed with restrictions: • preventive treatment of migraine (prescription or OTC medication recommended by a health care professional) is allowed provided the dose and regimen has been stable for at least 12 weeks prior to the Screening Visit and expected to be maintained until the EoS Visit (Week 24) Disallowed: • do not use oral anti-CGRPs for acute treatment <4 weeks prior to the Screening Visit and until EoS Visit (Week 24) • do not use eptinezumab or other mAb targeting the CGRP pathway <24 weeks prior to the Screening Visit and until EoS Visit (Week 24). • 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 until EoS Visit (Week 24) • do not use monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, or nimesulide <12 weeks prior to the Screening Visit and until EoS Visit (Week 24) • do not use injectable therapy (trigger point injections, extracranial nerve blocks, or facet joint injections) <8 weeks prior to the Screening Visit and until EoS Visit (Week 24)
Hormones	Hormonal therapy (for example, contraceptives, hormone replacement therapy) is allowed provided the dose and regimen has been stable for at least 12 weeks prior to the Screening Visit and expected to be maintained until the EoS Visit (Week 24).
Opioid analgesics	Prescription opiates (including single-ingredient or combination medications containing opiates, opioids, tramadol, or tapentadol) are allowed provided a stable dose and regimen has been maintained for at least 12 weeks prior to the Screening Visit for acute and/or symptomatic treatment of headache. These agents may be prescribed when considered medically indicated by the investigator during the study (including the screening period).

Drug Class	Details
Other interventions and devices	Allowed with restrictions: • non-pharmacological interventions and therapies for the treatment of migraine (for example, behavioural therapy, massage, and acupuncture) are allowed provided their use has been stable for at least 12 weeks prior to the Screening Visit and expected to be maintained until the EoS Visit (Week 24). Disallowed: • do not use CNS- and migraine-related devices (neuromodulation, neurostimulation) <8 weeks prior to the Screening Visit and until the EoS Visit (Week 24)
Sedatives/hypnotics	Barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) are allowed provided a stable dose and regimen has been maintained for at least 12 weeks prior to the Screening visit and expect to be maintained until the EoS Visit (Week 24). These agents may be prescribed when considered medically indicated by the investigator during the study (including the screening period) and a stable dose and regimen is expected to be maintained.
Traditional herbal medicines for the treatment of migraine	Allowed for the treatment of migraine providing a stable regimen has been maintained for at least 12 weeks prior to the Screening Visit and maintained until the EoS Visit (Week 24).
COVID-19 vaccines	Allowed during the study with the following guidance if possible: • a time window of at least 14 days should be allowed between COVID-19 vaccination and prior to the Screening Visit. • if the patient has recently received a COVID-19 vaccine, the investigator should judge if the patient can be administered with the IMP infusion at the scheduled visit based upon the patient's individual response to the COVID-19 vaccine. • COVID-19 vaccine should not be given within ±3 days of the IMP infusion.

Appendix III
Interpretation of Hepatitis B Serologic Test Results

Interpretation of Hepatitis B Serologic Test Results

HBsAg	negative	Susceptible
anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Immune due to natural infection
anti-HBc	positive	
anti-HBs	positive	
HBsAg	negative	Immune due to hepatitis B vaccination
anti-HBc	negative	
anti-HBs	positive	
HBsAg	positive	Acutely/Chronically infected
anti-HBc	positive	
anti-HBs	negative	
HBsAg	negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection
anti-HBc	positive	
anti-HBs	negative	