Clinical Study Protocol

Interventional, randomized, double-blind, parallel-group, placebo-controlled study of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments

Lu AG09222

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Synopsis – Study 19678A

Sponsor	**Investigational Medicinal Product**
H. Lundbeck A/S	Lu AG09222

Study Title

Interventional, randomized, double-blind, parallel-group, placebo-controlled study of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments

Objectives	**Endpoints**
Primary Objective • To evaluate the efficacy of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments	• Primary Endpoint: – Change from baseline in the number of monthly migraine days (MMDs) (Weeks 1 to 4) • Secondary Endpoints: – 50% MMD response: ≥50% reduction from baseline in MMDs (Weeks 1 to 4) – Change from baseline in the number of monthly headache days (MHDs) (Weeks 1 to 4) • CCI [redacted]

Objectives	Endpoints
Primary Objective (continued)	– CCI

Objectives	Endpoints
CCI	[redacted]

CCI [redacted]	[redacted]
Safety Objective • To evaluate the safety and tolerability of Lu AG09222	**Safety Endpoints** • Adverse events • Physical examination • Absolute values and changes from baseline in clinical safety laboratory test values, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), weight, and electrocardiograms (ECGs) • Potentially clinically significant safety laboratory test values, vital signs, weight changes, and ECG parameter values • Development of specific anti-drug antibodies (ADA) including neutralising antibodies • Columbia-Suicide Severity Rating Scale score

Study Methodology

- This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled Phase IIa study designed to demonstrate proof-of-concept, that is, to investigate whether the inhibitory action of Lu AG09222 on the PACAP pathway can be an effective mechanism for migraine prevention.
- The target population for this study is defined as patients diagnosed with migraine as outlined in the International Classification of Headache Disorders Third Edition (ICHD-3) guidelines,[1] with documented evidence of migraine occurring on CCI [redacted] per month prior to screening, as confirmed via prospectively collected information in the electronic diary (eDiary) during the screening period and with documented evidence of failure of 2 to 4 different preventive migraine medications in the past 10 years. Patients with a concurrent diagnosis of medication overuse headache (MOH) are allowed in the study.
- The aim is that approximately 30% of the randomized patients will have episodic migraine (EM; patients with headache occurring on <15 days). This will be ensured through a cap on the number of randomized EM patients. CCI [redacted]
- A total of 230 patients, recruited from specialist settings, will be randomly allocated via a randomization system to one of three treatment groups: Lu AG09222 CCI [redacted] Lu AG09222 CCI [redacted] or placebo, in a ratio of 2:1:2.
- Randomization will be stratified by region (North America versus Europe) and CCI [redacted]
- The total study duration from the Screening Visit to the Safety Follow-up Visit is approximately 16 weeks and includes a screening period (28 to 30 days), treatment period (4 weeks), and safety follow-up period (8 weeks).
- Patients will receive the investigational medicinal product (IMP) in the form of a single-dose administration at the Baseline Visit with either Lu AG09222 or placebo by intravenous (IV) infusion over 30 minutes (+15 minutes).
- Patients will complete a daily headache eDiary from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit.
- During the Baseline Visit, assessments of safety will be performed before and after the infusion. At this visit, adverse event details will be collected as well as safety laboratory test results, ECG results, weight, vital signs findings, and blood samples (CCI [redacted] ADA including NAb, and optional CCI [redacted] On the Baseline Visit day, patient-reported outcomes (PROs) must be completed prior to infusion. Patients must complete the eDiary recording of headaches that ended prior to infusion (i.e., for headaches which are ongoing or not yet recorded in the eDiary).

- Patients who complete the study will attend a Safety Follow-up Visit at 8 weeks after the Primary Outcome Visit.
- Patients who withdraw prior to the Primary Outcome Visit (Week 4), except for those who withdraw their consent, will have a Withdrawal Visit as soon as possible, an Efficacy Follow-up (Phone Contact) Visit at Week 4, and a further Safety Follow-up Visit at 12 weeks after administration of the IMP (the Baseline Visit). If the Withdrawal Visit takes place at Week 4, an Efficacy Follow-up (Phone Contact) Visit at Week 4 is not required.
- CCI [redacted]
- The study design is presented in Panel 1 (including the study periods) and the scheduled study procedures and assessments are summarized in Panel 2.
- An independent Safety Data Monitoring Committee (DMC) will regularly monitor the safety data according to the DMC Charter.

Number of Patients Planned

A total of 230 patients are planned for randomization: 92 in the Lu AG09222 CCI [redacted] group, 46 in the Lu AG09222 CCI [redacted] group, and 92 in the placebo group.

Target Patient Population

Main Inclusion Criteria

- The patient has a diagnosis of migraine as defined by ICHD-3 guidelines (section 1.1 Migraine without Aura, or 1.2 Migraine with Aura, or 1.3 Chronic Migraine)[1] confirmed at the Screening Visit.
- The patient has a history of migraine onset at least 12 months prior to the Screening Visit.
- The patient has a migraine onset at ≤50 years of age.
- The patient has CCI [redacted] per month for each month within the past 3 months prior to the Screening Visit.
- The patient fulfils the following criteria for migraine in prospectively collected information in the eDiary during the screening period:
  - Migraine occurring on CCI [redacted] and headache occurring on ≤26 days.
- 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 documented evidence of treatment failure* (must be supported by medical record or by treating physician's confirmation specific to each treatment) in the past 10 years of at least 2 to 4 (maximum) different migraine preventive medications out of the following:
  - Calcitonin gene-related peptide (CGRP)-directed therapies (monoclonal antibodies or gepants)**
  - Propranolol/metoprolol
  - Topiramate
  - Amitriptyline
  - Flunarizine
  - Candesartan
  - Valproate/divalproex
  - Botulinum toxin (if documented that botulinum toxin was taken for chronic migraine [CM])

- The patient is aged ≥18 and ≤65 years at the Screening Visit.

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

CCI [redacted]

Main Exclusion Criteria

- The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, chronic low back pain, complex regional pain syndrome).
- The patient has a diagnosis of acute or active temporomandibular disorder.
- The patient has a history or diagnosis of chronic tension-type headache, cluster headache, headache attributed to trauma or injury to the head and/or neck, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua, primary thunderclap headache, primary stabbing headache, nummular headache, new daily persistent headache, hypnic headache, trigeminal neuralgia, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura, or migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
- The patient has a lifetime history of psychosis, bipolar mania, or dementia. Patients with other psychiatric conditions whose symptoms are not controlled or who have not been adequately treated for a minimum of 6 months prior to screening are also excluded.
- The patient has a history of clinically significant cardiovascular disease, including uncontrolled hypertension, vascular ischaemia, or thromboembolic events (for example, cerebrovascular accident, deep vein thrombosis, or pulmonary embolism).
- The patient has 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 (including autoimmune), rheumatological, or ocular disorders.

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

- Disallowed: any investigational products within 30 days or 5 plasma half-lives (whichever is longer) before the Screening Visit; preventive migraine treatments; oral anti-CGRP treatment; central nervous system- and migraine-related devices (neuromodulation, neurostimulation) or injectable therapies (such as trigger point injections, extracranial nerve blocks, or facet joint injections); botulinum toxin; or monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, or nimesulide; immunosuppressants (e.g., steroids).
- Allowed with restriction: prescription or over-the-counter medication for acute treatment of migraine prescribed or recommended by a healthcare professional; hormonal therapy (for example, contraceptives, hormone replacement therapy); anti-impotence agents; barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital); prescription opiates (including single-ingredient or combination medications containing opiates, opioids, tramadol, or tapentadol); nicotine, tobacco and cannabinoids; benzodiazepines; steroids, and non-pharmacological interventions and therapies; vaccinations.

Investigational Medicinal Products, Doses and Modes of Administration

Lu AG09222 – CCI [redacted] solution for injection/infusion CCI [redacted] added to 0.9% normal saline CCI [redacted] IV.

Placebo – 100 mL of 0.9% normal saline, IV.

The IMP will be administered by IV infusion over 30 minutes (+15 minutes).

Assessment Details

The assessments are summarized in Panel 2. Details for clinical outcome and CCI [redacted] assessments are provided below.

eDiary

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

CCI


CCI

CCI

Blood samples for CCI will be analysed according to methods described in the study-specific *Laboratory Specification*. The CCI are as follows:

- CCI
- CCI
- CCI
- CCI

*CCI

**CCI will be analysed as part of the Clinical Safety Laboratory Panel.

CCI

Statistical Methodology

The following analysis sets will be used for the analyses:

- *All patients enrolled set (APES)* – all enrolled patients
- *All patients randomized set* (*APRS*) – all randomized patients
- *All patients treated set (APTS)* – all patients in the APRS who received an infusion of the IMP
- *Full analysis set (FAS)* – all patients in the APTS who have a valid baseline assessment of the number of MMDs and a valid assessment of MMDs over Weeks 1 to 4
- *Full analysis set long term (FAS-LT)* – all patients in the APTS who have a valid baseline assessment of the number of MMDs and at least one valid post-baseline assessment of MMDs (Weeks 1 to 4 or Weeks 5 to 8 or Weeks 9 to 12)
- CCI
- Safety results will be reported based on the APTS. Efficacy results in the treatment period will be reported for the FAS. Maintenance of effect covering efficacy in the Treatment as well as the safety follow-up period will be reported for the FAS-LT.
- Unless otherwise specified, all testing will be one-sided, based on a 5% significance level.
- In relation to estimands, the following intercurrent events (IEs) have been identified:
  - Use of acute rescue medication
  - Use of preventive migraine therapy
  - Treatment not administered per protocol
- Primary analysis of the primary endpoint:
  - Clinical question to be answered: Does Lu AG09222 prevent migraine in the target patient population?
  - Estimand: The primary estimand will be the effect of Lu AG09222 that would be seen regardless of whether treatment was administered per protocol and if no preventive migraine therapy was used and all patients were able to continue in the study.
  - Treatment: The treatment of interest is Lu AG09222 and the reference treatment is placebo.
  - Population: The FAS including the target population as described above.
  - Variable: Change from baseline in the number of MMDs over Weeks 1 to 4, which summarizes eDiary data across Weeks 1 to 4. If acute rescue medication is used successfully during a day, this day counts as a migraine day (details will be given in the *Statistical Analysis Plan* [SAP]). Details on the imputation strategy for missing diary data will be described in the protocol.

– Intercurrent events: The IEs are defined above. Use of acute rescue medication or preventive migraine therapy (different from investigational medication) is taken into account using a composite strategy. Incorrect administration of treatment is handled using a treatment policy strategy. The IE "use of preventive migraine therapy" will be addressed with a hypothetical strategy. If withdrawal from study occurred, data obtained after withdrawal will be included in the analysis, and, if IEs occur after withdrawal from study (use of acute rescue medication or preventive migraine therapy), the methods described for handling IEs will be applied. Full details of the statistical methods for handling IEs and missing data, will be described in the SAP.
– Population level summary (primary analysis): The least-squares mean difference in change from baseline in the number of MMDs (Weeks 1 to 4) between the high dose of CCI and placebo, based on an analysis of covariance (ANCOVA) with baseline MMDs as covariate and treatment (placebo, low dose, high dose), population (EM or CM), and an interaction between the stratification factors (region and CCI [redacted]

- Sensitivity analyses of the primary endpoint:
  – The impact of the imputation of the primary endpoint will be assessed in a sensitivity analysis, applying different measures of imputation. For patients experiencing an IE, the imputation strategy will depend on the type of IE.
  – 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.

Testing Strategy

The type 1 error will only be controlled for the primary analysis comparing the primary endpoint (change from baseline in MMDs [Weeks 1 to 4]) for the high dose of Lu AG09222 to placebo at a one-sided 5% significance level. Other analyses will be considered exploratory, and statistical significance will be considered indicative, rather than confirmative, for the finding.

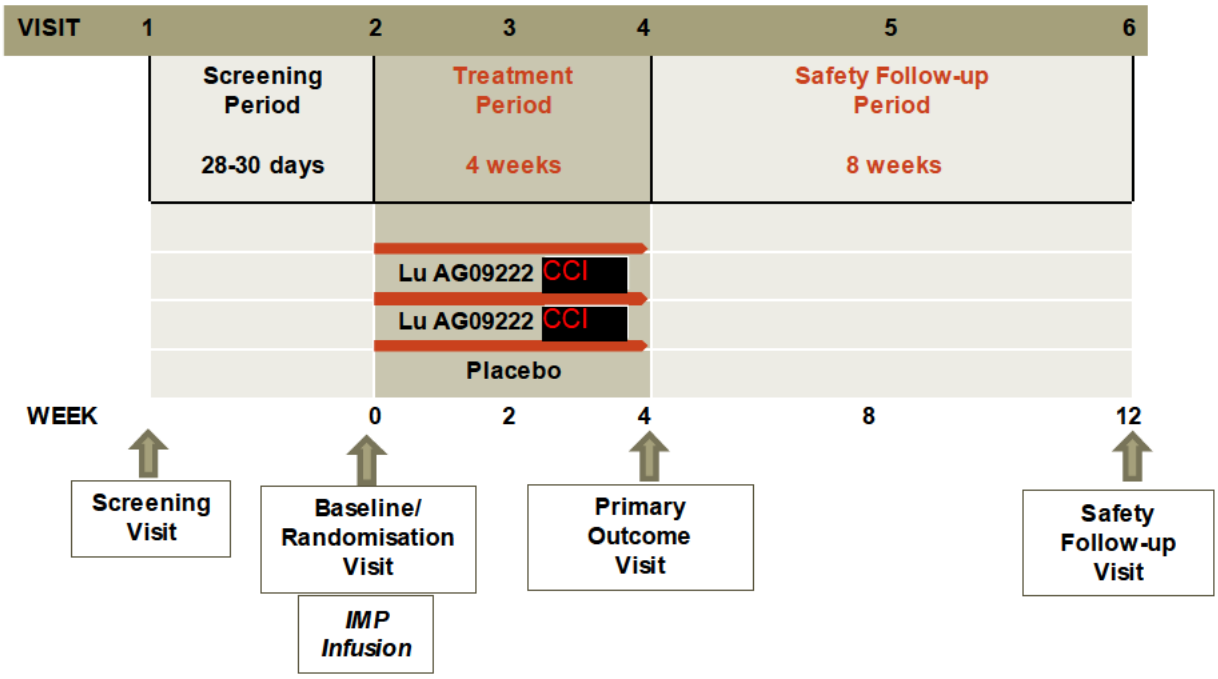
Sample Size Considerations

Simulations were used to determine a sample size that ensured at least 80% power at a one-sided 5% significance level for detecting an effect of 2.1 on the CCI dose when using an ANCOVA with baseline MMD as a covariate and treatment and population (EM or CM) as fixed factors. A population with 30% EM and 70% CM patients was assumed with standard deviations of 3.8 and 6.1, respectively, which resulted in a standard deviation of 5.6 for the full population. The resulting required sample size is 86 patients per arm for the CCI dose and placebo. No formal power calculation was performed for the CCI dose. A sample size of 43 patients per arm was considered sufficient to evaluate the relevant endpoints for this dose, which results in a randomization ratio of 2:1:2. Adjusting for an expected 5% dropout rate, a total sample size of 230 will be required.

The cap of 30% for the EM population results in a similar precision (standard error) for the treatment estimates for the EM and CM populations.

Simulations are based on 10000 runs.

Panel 1 Study Design



IMP = investigational medicinal product.

The study consists of a screening period (28 to 30 days), a treatment period (4 weeks), and a safety follow-up period (8 weeks). IMP (Lu AG09222 CCI Lu AG09222 CCI or placebo) will be administered by intravenous infusion at the Baseline Visit. At Week 4, patients will complete the Primary Outcome Visit and will return to the clinic 8 weeks later for a Safety Follow-up Visit.

Panel 2 Study Procedures and Assessments

Visit Name	Screening	Baseline + IMP		Primary Outcome		Safety Follow-up	Withdrawal[c]	Efficacy Follow-up (telephone contact)[c]
Visit Number	**1 SCR**	**2 BL**	**3**	**4 PO**	**5**	**6 SFU**	**WD**	**EFU**
Type of Visit[x]	**Clinic**	**Clinic**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic**	**Clinic /Tele visit/ Home**	**Telep hone**
Day/End of Week[a]	**-4**	**0**	**2**	**4**	**8**	**12**		**4**
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±5**		**±2**
Screening and Baseline Procedures and Assessments								
Signed informed consent form	√							
Separate informed consent forms (optional)	√							
Demographics (age, sex, race)	√							
Diagnosis	√							
Disease-specific history[d]	√							
Relevant history (social, medical, psychiatric, neurological)	√							
Documented evidence of previous failure of 2-4 migraine preventive medications[e]	√							
Recent medication (prescription and non-prescription), herbal remedies, non-pharmacological interventions, vitamin and mineral supplements	√							
Height	√							
Blood sampling for serology (HBsAg, anti-HBs, anti-HBc, and anti-HCV)	√							
Blood sampling for other screening (e.g., β-hCG, FSH)	√							
Urine drug screen and alcohol screen	√							
Inclusion/exclusion criteria	√	√						
Signs and symptoms present at Screening and Baseline (before IMP administration) (recorded on an *Adverse Event Form*)	√	√						
CCI		√[j]						
Randomization		√						
Efficacy Assessments								
eDiary daily recording[f,g]	√	√[j]	√	√	√	√[c,k]	√[k]	√[k]

Visit Name	Screening	Baseline + IMP		Primary Outcome		Safety Follow-up	Withdrawal[c]	Efficacy Follow-up (telephone contact)[c]
Visit Number	**1 SCR**	**2 BL**	**3**	**4 PO**	**5**	**6 SFU**	**WD**	**EFU**
Type of Visit[x]	**Clinic**	**Clinic**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic**	**Clinic /Tele visit/ Home**	**Telep hone**
Day/End of Week[a]	**-4**	**0**	**2**	**4**	**8**	**12**		**4**
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±5**		**±2**
eDiary compliance check[f,h]		√	√	√	√	√[c]	√	√
CCI								
Pharmacokinetic Assessments								
Blood sampling for CCI quantification		√[l]	√	√	√	√	√	
Exploratory Pharmacodynamic Assessments								
Blood sampling for CCI		√[l]	√	√	√	√	√	
Blood sampling for CCI		√[m]		√				
Blood sampling for CCI		√[m]		√				
Safety Assessments								
Adverse events	√	√[m,n,o]	√	√	√	√	√	√
Blood and urine sampling for clinical safety laboratory tests	√	√[m]	√	√	√	√	√	
Blood sampling for ADA including NAb		√[m]	√	√	√	√[p]	√	
Vital signs (including body temperature), weight, ECGs	√	√[m,n]	√	√	√	√	√	
Examinations (physical)[q]	√	√[m]		√		√	√	
Examinations (neurological)[q]	√	√[m]				√		
C-SSRS[r]	√	√[m]	√	√	√	√	√	

Visit Name	Screening	Baseline + IMP		Primary Outcome		Safety Follow-up	Withdrawal[c]	Efficacy Follow-up (telephone contact)[c]
Visit Number	**1 SCR**	**2 BL**	**3**	**4 PO**	**5**	**6 SFU**	**WD**	**EFU**
Type of Visit[x]	**Clinic**	**Clinic**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic /Tele visit/ Home**	**Clinic**	**Clinic /Tele visit/ Home**	**Telep hone**
Day/End of Week[a]	**-4**	**0**	**2**	**4**	**8**	**12**		**4**
Visit Window[b] (days relative to nominal visit)	**-2**		**±2**	**±2**	**±2**	**±5**		**±2**
Biobanking								
CCI								
Other Study Procedures and Assessments								
IMP administered (IV infusion)[t]		√[u]						
IMP accountability[v]		√						
Concomitant medication (prescription and non-prescription), herbal remedies, non-pharmacological interventions, vitamin, and mineral supplements		√[m]	√	√	√	√	√	√
Substance use (alcohol, tobacco, caffeine, marijuana)		√[m]		√		√	√	
eDiary training[f]	√							
PRO training[f]	√							
eDiary closeout[k]						√	√	√
Pregnancy test[w]	√	√[m]		√		√	√	
CCI						√		

ADA = anti-drug antibodies; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; anti-HCV = hepatitis C virus antibody; CCI -SSRS = Columbia-Suicide Severity Rating Scale; CCI ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EFU = efficacy follow-up; CCI FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; CCI IMP = investigational medicinal product; IV = intravenous; CCI MOH = medication overuse headache; CCI NAb = neutralizing antibodies; CCI CCI PO = primary outcome; PRO = patient-reported outcome; CCI SCR = screening; SFU = safety follow-up; WD = withdrawal

a. All assessments may be completed over a maximum of 2 consecutive days with the exception of PROs (see footnote i below); if so, the first day is considered the "visit" day according to the schedule.
b. If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit.
c. Patients who withdraw prior to the Primary Outcome Visit (Week 4), except for those who withdraw their consent, will have a Withdrawal Visit as soon as possible, an Efficacy Follow-up (Phone Contact) Visit at Week 4, and a further Safety Follow-up Visit scheduled 12 weeks after administration of the IMP (the Baseline Visit). At the Safety Follow-up Visit, patients will not be required to complete efficacy assessments. The eDiary assessments should continue on a daily basis until Week 4:
   - If the Withdrawal Visit takes place during the treatment period and prior to Week 3, the patient will be contacted via phone for an Efficacy Follow-up (telephone contact) Visit at Week 4 for the eDiary closeout.
   - If the patient withdraws between Week 3 and Week 4, then the Withdrawal Visit should be scheduled at Week 4 for the eDiary closeout and thus an Efficacy Follow-up (telephone contact) Visit at Week 4 is not required.
d. Patients must have adequately documented records of their previous migraine history. Patients with a concurrent diagnosis of MOH are allowed in the study (at the Screening Visit, the investigator must confirm whether or not the patient has a concurrent diagnosis of MOH).
e. The patients must have documented evidence of failure in the past 10 years of at least 2 to 4 (maximum) different pharmacological migraine preventive medications. Acceptable documentation of previous treatment failures includes (i) medical record with medication's name, stop and start dates, dose level, and reasons for discontinuation or (ii) treating physician's confirmation specific to each treatment – see chapter 12.
f. At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary and PROs. Details will be provided in a separate site information guide.
g. The eDiary assessments will be completed in the remote setting on a daily basis.
h. In addition to the eDiary compliance checks performed at the defined visits, 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.
i. PROs scheduled at the Baseline Visit (Visit 2) must be completed in the clinic at the visit date and before the infusion. PROs that are scheduled in alignment with the other visits can be completed on the day or within 3 days prior to the scheduled visit date.
j. Patients must complete the PRO entries prior to infusion. Patients must complete the 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 the Safety Follow-up Visit while the patient is at the site. For patients who withdraw prior to the Primary Outcome Visit (Week 4), except for those who withdraw their consent, the eDiary closeout will take place at the Efficacy Follow-up (Phone Contact) Visit at Week 4 (or at the Withdrawal Visit if scheduled at Week 4). Details will be provided in separate training material.
l. Multiple samples for CCI are to be taken relative to IMP infusion: prior to infusion, immediately after the end of infusion (EOI) and 2 hours after EOI.
m. The following must be collected/completed prior to infusion: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), concomitant medications, substance use, AEs, physical and

neurological examinations, ECG, blood sampling (for clinical safety laboratory tests, CCI [redacted] ADA including NAb, and optional CCI [redacted] urine sampling (for clinical safety laboratory and pregnancy tests), CCI [redacted] and C-SSRS. Vital signs must be assessed prior to blood sampling.

n. The following must be collected after infusion: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), AEs and blood sampling for CCI [redacted] Vital signs must be assessed prior to blood sampling.

o. Infusion-related reactions must be checked as part of the overall AE collection, during and after infusion, and before the patient is discharged from the site.

p. A proportion of patients who complete the Safety Follow-up Visit (Week 12) will be asked to provide additional blood samples for post-study immunogenicity testing at 12-week intervals (potentially up to 12 months relative to the infusion date). The number of patients from whom these samples will be collected will be decided during the study in consultation with the sponsor.

q. For the Baseline Visit, examinations must be performed prior to the infusion.

r. The CCI [redacted] and C-SSRS will be administered by the authorized rater. For this study, the following versions of the C-SSRS scale are used: the "Baseline/Screening" will be used at the Screening Visit and the "Since last visit" version will be used for all subsequent visits.

s. CCI [redacted]

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

u. Patients must be monitored during the infusion and for a period of 2 hours from the EOI. Patients will be requested to stay longer should the investigator or designee determine this is clinically warranted.

v. A designated unblinded clinical research associate is responsible for IMP accountability.

w. For women of childbearing potential, a pregnancy test at the Screening Visit and the Safety Follow-up Visit is to be conducted using serum β-hCG. At Visit 2, Visit 4 and Withdrawal Visit, urine pregnancy testing will be performed, and, in case of a positive finding, further confirmatory testing will be performed via serum β-hCG.

x. Visit 3, Visit 4 (Primary Outcome Visit), Visit 5 and Withdrawal Visit can be conducted as a clinic visit to the site by the patient **or** can be provided as a home visit by a healthcare provider/study site staff with or without a televisit through teleconferencing. Before these visits are conducted, patients will have the option to choose the types of visits to be conducted and these are allowed to be changed during the study. The type of visits conducted must be recorded in the eCRF. Further information on the type of visits will be provided in the *Site Guide for Off-Site Nursing Services and TeleVisit Solutions Site Reference Guide*.

y. CCI [redacted]

Table of Contents

List of Panels **23**

List of Abbreviations and Definitions of Terms **24**

Major Changes Since Last Edition **27**

1 Introduction **28**
1.1 Background 28
1.1.1 Overview 28
1.1.2 Nonclinical Data 29
1.1.2.1 Primary Pharmacology 29
1.1.2.2 Safety Pharmacology 30
1.1.2.3 Pharmacokinetics and Metabolism 30
1.1.2.4 Toxicology 30
1.1.3 Clinical Data 31
1.2 Rationale for the Study 32

2 Objectives and Endpoints **33**

3 Study Design **36**
3.1 Overview of the Study Design 36
3.2 Rationale for the Study Design 38

4 Ethics **40**
4.1 Ethical Rationale 40
4.2 Informed Consent 41
4.3 Personal Data Protection 42
4.4 Ethics Committee(s) and Institutional Review Board(s) 43

5 Study Population **43**
5.1 Number of Patients and Countries 43
5.2 Patient Recruitment 43
5.3 Selection Criteria 43
5.4 Withdrawal Criteria 48

6 Investigational Medicinal Products **48**
6.1 Treatment Regimen 48
6.2 IMP, Formulation and Strength 48
6.3 Manufacturing, Packaging, Labelling, and Storage of IMP(s) 49
6.4 Method of Assigning Patients to Treatment 50
6.5 IMP Accountability 50
6.6 Unblinding Procedures 50
6.7 Post-study Access to IMP(s) 50

7 Concomitant Medication **51**

8 Study Visit Plan **51**
8.1 Overview 51
8.2 Screening Visit (Visit 1) 52
8.2.1 Pre-screening 53
8.2.2 Patient Identification Card 53
8.2.3 Re-screening 53

8.3 Baseline + IMP Visit (Visit 2) 54
8.4 Visit 3 55
8.5 Primary Outcome Visit (Visit 4) 56
8.6 Visit 5 56
8.7 Safety Follow-up Visit (Visit 6) 57
8.8 Unscheduled Visit 58
8.9 Withdrawal Visit 58
8.10 Efficacy Follow-up Visit (Telephone Contact) 60
8.11 End-of-study Definition 60

9 Assessments 60
9.1 Screening and Baseline Procedures and Assessments 60
9.1.1 Demographics and Baseline Characteristics 60
9.1.2 Diagnostic Assessments 61
9.1.3 Classifications for Eligibility 62
9.1.4 Drug and Alcohol Screen 64
9.2 Efficacy Assessments 64
CCI [redacted] CCI [redacted] CCI
9.2.1.2 eDiary 65
CCI [redacted]
..... 69
9.3 Pharmacokinetic Assessments 69
9.4 Pharmacodynamic Assessments 70
9.4.1 Blood Sampling for Exploratory CCI Assessments 70
9.4.2 Blood Sampling for Exploratory CCI [redacted] Assessments 70
9.4.3 Blood Sampling for Exploratory CCI [redacted] 70
9.5 Safety Assessments 71
9.5.1 Adverse Events 71
9.5.2 Clinical Safety Laboratory Tests 71
9.5.3 Vital Signs 72
9.5.4 Height and Weight 73
9.5.5 Electrocardiograms 73
9.5.6 Physical and Neurological Examinations 73
9.5.7 Columbia-Suicide Severity Rating Scale 74
9.5.8 Anti-drug Antibody Including Neutralizing Antibody Assessments 75
9.6 Other Assessments 75
CCI [redacted] CCI [redacted]
9.7 Biobanking 77
CCI [redacted]

CCI [redacted]
9.8 Order of Assessments ... 79
9.9 Total Volume of Blood Drawn and Destruction of Biological Material ... 80
9.10 Treatment Compliance ... 80

10 Adverse Events ... 81
10.1 Definitions ... 81
10.1.1 Adverse Event Definitions ... 81
10.1.2 Adverse Event Assessment Definitions ... 82
10.1.3 Study-specific Adverse Event Definitions ... 83
10.1.3.1 Infusion-related Reactions ... 83
CCI [redacted]
10.2 Pregnancy ... 84
10.3 Recording Adverse Events ... 84
10.4 Reporting Serious Adverse Events ... 84
10.5 Treatment and Follow-up of Adverse Events ... 85
10.6 Data Monitoring Committee ... 86

11 Data Handling and Record Keeping ... 86
11.1 Data Collection ... 86
11.1.1 Electronic Case Report Forms ... 86
11.1.2 Patient Binders ... 86
11.1.2.1 Use of Patient Binders ... 86
11.1.2.2 Serious Adverse Event Fallback Forms ... 87
11.1.3 External Data ... 87
11.2 Database Release ... 87
11.3 Retention of Study Documents at the Site ... 87
11.3.1 eCRF Data ... 87
11.3.2 Other Study Documents ... 88

12 Monitoring Procedures ... 88

13 Audits and Inspections ... 89

14 Protocol Compliance ... 89

15 Study Termination ... 90

16 Statistical Methodology ... 90
16.1 Responsibilities ... 90
16.2 Analysis Sets ... 90
16.3 Descriptive Statistics ... 91
16.4 Patient Disposition ... 91
16.5 Demographics and Baseline Characteristics ... 91
16.6 Recent and Concomitant Medication ... 91
16.7 Exposure ... 91
16.8 Efficacy Analyses ... 92
16.8.1 General Efficacy Analysis Methodology ... 92
16.8.2 Primary Analysis of the Primary Endpoint ... 92
16.8.3 Sensitivity Analyses of the Primary Endpoint ... 93
16.8.4 Testing Strategy ... 93
16.8.5 Analysis of the Secondary Endpoints ... 93

16.8.6 Analysis of the Exploratory Endpoints 93
16.8.7 Analysis of Subgroups 94
16.9 Safety Analyses 94
16.9.1 Analysis of Adverse Events 94
16.9.2 Analysis of Other Safety Endpoints 95
16.10 Sample Size and Power 95
16.11 Statistical Analysis Plan 95

17 Clinical Study Report and Publications 96
17.1 Data Ownership 96
17.2 Clinical Study Report 96
17.3 Summary of Clinical Study Results 96
17.4 Publications 96

18 Indemnity and Insurance 96

19 Finance 96
19.1 Site Agreements 96
19.2 Financial Disclosure 97
19.3 Equipment 97

References 98

Appendices

Appendix I Clinical Study Protocol Authentication and Authorization 102
Appendix II Recent and Concomitant Medication Disallowed or Allowed with Restrictions 104
Appendix III Interpretation of Hepatitis B Serologic Test Results 108

List of Panels

Panel 1 Study Design....12
Panel 2 Study Procedures and Assessments....13
Panel 3 Objectives and Endpoints....33
Panel 4 ICHD-3 Guidelines for Migraine....62
Panel 5 Clinical Safety Laboratory Tests....71

List of Abbreviations and Definitions of Terms

ADA	anti-drug antibodies
ANCOVA	analysis of covariance
anti-HCV	hepatitis C virus antibody
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
APRS	all patients randomized set
APTS	all patients treated set
CCI [redacted]	[redacted]
β-hCG	beta-human chorionic gonadotropin
CCI [redacted]	[redacted]
BMI	body mass index
BSC	best supportive care
CC [redacted]	[redacted]
CCI [redacted]	[redacted]
CGRP	calcitonin gene-related peptide
CI	confidence interval
ClinRO	clinician-reported outcome
CM	chronic migraine
C_{max}	maximum observed concentration
CNS	central nervous system
CCI [redacted]	[redacted]
COA	clinical outcome assessment
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DBL	database lock
DMC	Data Monitoring Committee
CCI [redacted]	[redacted]
DSM-5®	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EOI	end of infusion
CCI [redacted]	[redacted]
EudraCT	European Union Drug Regulating Authorities Clinical Trials

FAS	full analysis set
FAS-LT	full analysis set long term
FIH	first-in-human
FSH	follicle-stimulating hormone
HBsAg	hepatitis B surface antigen
CCI	[redacted]
CCI	[redacted]
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3	International Classification of Headache Disorders Third Edition
ICMJE	International Committee of Medical Journal Editors
IE	intercurrent event
IHS	International Headache Society
IMP	investigational medicinal product
IRB	institutional review board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous(ly)
CCI	[redacted]
Lu	Lundbeck
CCI	[redacted]
CCI	[redacted]
MHD	monthly headache day
MMD	monthly migraine day
MMRM	mixed model for repeated measurements
MOH	medication overuse headache
CCI	[redacted]
NAb	neutralizing antibodies
CCI	[redacted]
CCI	[redacted]
PCR	polymerase chain reaction
PD	Pharmacodynamic(s)
CCI	[redacted]
PK	pharmacokinetic(s)
PoC	proof-of-concept
popPK	population pharmacokinetic(s)
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
QP	qualified person
QRS	specific ECG interval describing ventricular depolarization
QT	specific ECG interval describing ventricular depolarization/repolarization

QTc	heart rate-corrected QT interval
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAE	serious adverse event
SAP	*Statistical Analysis Plan*
SC	subcutaneous(ly)
SPG	sphenopalatine ganglion
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TMF	trial master file
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]

Major Changes Since Last Edition

All descriptions of and references to the non-binding interim analysis for futility are removed across the *Clinical Study Protocol*, as the interim analysis for futility will not be conducted as informed to sites as per memo *19678A Interim Analysis for Futility* (dated 20-06-2022). Minor wording clarifications/edits are also made in particular in *Appendix II: Recent and Concomitant Medication, Disallowed or Allowed with Restrictions*.

1 Introduction

1.1 Background

1.1.1 Overview

Migraine is a disabling disorder characterized by moderate-severe headache which is often accompanied by nausea, vomiting, photophobia, and phonophobia.[1] Attacks of migraine typically last between 4 and 72 hours, produce significant disability, and recur often. Migraine is more common in women and most prevalent through the third and fourth decades of life, amplifying its impact on family and career development.[2] Migraine is one of the most prevalent neurological diseases for which medical treatment is sought and worldwide is considered the leading cause of disability for people under the age of 50.[3,4]

Generally, migraine begins as an episodic disease. Between attacks of migraine, the nervous system returns to a normal (premorbid) state of function. However, among patients with episodic migraine (EM), approximately 2.5% per year progress to chronic migraine (CM), that is, headache on 15 days or more a month of which 8 are migraine attacks, for at least 3 consecutive months.[1,5,6] In CM, headaches are more frequent and migraine-related life impact and disability are much greater than those observed in EM. In addition, CM has a stronger association with co-morbid conditions such as anxiety, depression, and non-headache pain.

Currently, pharmacological treatments of migraine include acute and preventive treatments. Preventive treatments are used on a sustained basis for periods of months to years to prevent migraine from occurring. Preventive treatment may be appropriate in a number of instances, including where frequency of attacks per month is 2 or higher or where a patient's quality of life is severely impaired.[7] Conventional preventive treatments belong to different pharmacological categories (e.g., beta-blockers, anticonvulsants) and were all initially developed for other conditions. These treatments show little efficacy and often poor tolerability in patients with migraine, resulting in frequent early discontinuation of treatment.[2,8,9,10,11,12,13] Furthermore, preventive treatment can take weeks to months to achieve optimal efficacy.[14,15] Thus, there is a need for preventive medications that are more effective and better tolerated than the current standard of care.[16] The high prevalence of migraine and its associated disability, especially when transformed to CM, are important justifications for developing effective treatments for the prevention of migraine. Establishing a robust and clinically meaningful migraine preventive effect as early as possible is a particularly important outcome for patients and is important for facilitating management and health resource decisions by healthcare professionals. This is highlighted in the recently published guidelines of the International Headache Society (IHS) for controlled studies of preventive treatment of EM and CM in adults where the onset of preventive treatment effect is recommended as a secondary endpoint.[17,18]

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a multifunctional neuropeptide that is implicated in migraine pathophysiology.[19,20,21,22,23] PACAP is expressed, along with its receptors, throughout the nervous system, including distinct areas suggestive of a role in

migraine pathophysiology such as the trigeminovascular system, trigeminal ganglia, trigeminal nucleus caudalis, dorsal horn of the spinal cord, brainstem, hypothalamus, pituitary, and the otic and sphenopalatine ganglions (SPGs).[24,25,26,27,28,29] PACAP exists in two forms, one composed of 38 amino acids (PACAP38) and another composed of 27 amino acids (PACAP27). Of the two forms, PACAP38 is the more prevalent, representing up to 90% of PACAP forms in mammalian tissues.[20]

A mechanistic role for PACAP38 in migraine is supported by several clinical observations: (1) an infusion of PACAP38 in patients with migraine without aura triggers migraine-like attacks (associated with photophobia, phonophobia, and nausea) and sustained vasodilation of extracranial arteries;[21,30,31] (2) PACAP38-induced migraine-like attacks respond to triptans;[32,33] (3) plasma concentrations of PACAP38 are elevated during spontaneous migraine attacks (ictal), as compared to inter-ictal levels;[33] and (4) in patients with migraine headache, plasma PACAP38 levels decrease after sumatriptan treatment correlating with headache amelioration.[34]

PACAP differs from calcitonin gene-related peptide (GCRP) in that it has greater SPG and parasympathetic involvement.[35] The SPG is considered to play a role in headache pain and cranial autonomic symptoms caused by activation of the trigeminal-autonomic reflex, which might entail the involvement of PACAP in the development of cranial autonomic symptoms. Moreover, chronic stress and pain paradigms upregulate the PACAP signalling axis, suggesting that PACAP may play a critical role in central neurocircuits that mediate pain and stress response behaviours.[36,37,38,39] Finally, PACAP acts as a mast cell degranulator with the ability to impact neurogenic inflammatory processes and central pain signalling and sensitization.[40,41]

Lu AG09222 is a humanized monoclonal antibody that inhibits the action of PACAP and is being developed by H. Lundbeck A/S for the treatment of conditions that may benefit from the inhibition of PACAP, including migraine. Lu AG09222 binds with high affinity to both PACAP38 and PACAP27, thus blocking signalling through the PACAP receptors (PAC1-R, VPAC1-R, and VPAC2-R) and inhibits endogenously released PACAP in vivo. Considering the clinical observations that support a mechanistic role for PACAP in migraine and the ability of Lu AG09222 to inhibit PACAP, Lu AG09222 may potentially provide efficacy in migraine populations based on a mechanism of action that differs from currently available preventive treatments for migraine.

The following sections provide a brief overview of the nonclinical and clinical data currently available for Lu AG09222. Refer to the current version of the Investigator's Brochure for further details.[42]

1.1.2 Nonclinical Data

1.1.2.1 Primary Pharmacology

PACAP and its receptors are expressed in multiple peripheral organs, as well as in the peripheral and central the nervous system.[43,44,45,46] Upon PACAP receptor binding, the receptors VPAC1-R, VPAC2-R, and PAC1-R all have the ability to cause intracellular

accumulation of cyclic adenosine monophosphate and downstream signalling.[47,48] In preclinical mechanistic studies, Lu AG09222 inhibited PACAP-associated lacrimation and facial temperature increases (as a surrogate for vasodilation) in an intranasally administered umbellulone-driven, trigemino-parasympathetic reflex activity model in rats. Furthermore, Lu AG09222 inhibited PACAP-induced photophobia in mice and PACAP-driven increases in dermal blood flow in cynomolgus monkeys. Together, these PD data in mice, rats, and cynomolgus monkeys support the antagonistic activity of Lu AG09222 against PACAP signalling in humans.

1.1.2.2 Safety Pharmacology

Safety pharmacology assessments in the pivotal repeat-dose toxicity studies revealed no Lu AG09222-related adverse effects on the central nervous system (CNS) in rats or monkeys or on cardiovascular and respiratory functions in cynomolgus monkeys.

1.1.2.3 Pharmacokinetics and Metabolism

In the toxicokinetic studies performed, exposure increased with increasing dose level in rats, rabbits, and cynomolgus monkeys receiving single or repeated doses of Lu AG09222 up to CCI per dose. CCI

As a monoclonal antibody, Lu AG09222 is not expected to undergo metabolism or transport as a clearance pathway, and its potential to affect or be affected by concomitant medication is therefore limited. Moreover, the mechanism of action is not related to cytokines, cytokine modulators, or other factors expected to impact cytochrome P450 enzymes. Consequently, nonclinical pharmacokinetic (PK) drug interaction studies have not been conducted.

1.1.2.4 Toxicology

The pivotal 4-week, repeat-dose toxicity studies were conducted in rats and cynomolgus monkeys using IV or subcutaneous (SC) administration, and the 26-week, repeat-dose toxicity study was conducted in cynomolgus monkeys using IV administration. In the 4-week study, administration of Lu AG09222 was well tolerated. There were no Lu AG09222-related changes in clinical signs, food consumption, body weight or body weight gain, or clinical pathology parameters or Lu AG09222-related effects on electrocardiology or blood pressure, heart rate, or respiratory rate at any of the dose levels tested (up to CCI

In the 26-week study, administration of Lu AG09222 was also generally well tolerated. CCI

There is a theoretical potential for Lu AG09222 to modulate inflammatory processes and thereby exacerbate immune complex-driven pathology, which should be considered during clinical administration.

Results from the nonclinical safety studies suggest that the risk associated with the administration of Lu AG09222 is low and support multiple-dose clinical administration with Lu AG09222 IV or SC.

1.1.3 Clinical Data

Lu AG09222 has been studied in the first-in-human (FIH) study (18902A) which is currently in the reporting phase. Thus, the data are preliminary and based on a cut-off date of 24 September 2020, corresponding to the database lock (DBL). This was a randomized, double-blind, placebo-controlled, single ascending dose Phase I study to determine the safety, tolerability, and PK of Lu AG09222. The study included healthy men and women aged 18 to 55 years and comprised two parts: a dose-escalating part (Part A) and an expanded-cohort part to assess the combination treatment of Lu AG09222 and sumatriptan (Part B). In Part A, 8 healthy men per cohort (Cohorts 1 to 7) were randomized (3:1) to Lu AG09222 IV in single ascending doses of CCI and CCI or placebo. Additionally, 8 healthy women (Cohort 8) were randomized (3:1) to Lu AG09222 IV to CCI or placebo. In Part B, 8 healthy men and 8 healthy women were randomized (1:1) in Cohort 9 to Lu AG09222 CCI IV (dose determined based on Part A) or placebo, both treatments in combination with sumatriptan 6 mg SC administered 2 hours after the end of the IV infusion. In Cohort 10, 8 healthy men and 8 healthy women were randomized (3:1) to Lu AG09222 CCI SC or placebo.

Preliminary safety data from the FIH study indicate that administration of Lu AG09222 in single doses of CCI and CCI in healthy subjects is generally safe and well tolerated. A total of 96 healthy subjects received placebo, Lu AG09222 IV or SC, Lu AG09222 IV plus sumatriptan SC, or placebo plus sumatriptan SC.

Of the 60 subjects treated with Lu AG0922 IV or SC, 32 had a total of 65 non-serious treatment-emergent adverse events (TEAEs), while 8 of 8 subjects treated with Lu AG09222 plus sumatriptan had a total of 17 TEAEs. No subjects died or withdrew due to adverse events during the study.

One serious adverse event (SAE) of Grade 2 [*moderate*] chilblains (perniosis) was reported. The first lesions were noted at approximately 5 half-lives after administration of Lu AG09222 CCI IV plus sumatriptan 6 mg SC. The SAE was considered *related* to Lu AG09222 and *not related* to sumatriptan by the investigator. The investigator considered cold exposure leading to abnormal vascular and nerve function in the extremities as a mechanism underlying the chilblains. Lundbeck considered the event *possibly related* to Lu AG09222 and considered the primary cause for this event to be cold exposure in a subject with a possible bug bite and a history of psoriasis, although a potential contribution of Lu AG09222 could not be excluded. The subject tested negative for ADA. The most common adverse events seen in more than 2 subjects were upper respiratory tract infection, headache, diarrhoea, liver function test abnormal, dizziness, dysmenorrhoea, and presyncope.

Most adverse events were *mild*. There was no pattern in the distribution of TEAEs across the doses of Lu AG0922 to indicate a causal relationship between the TEAEs and Lu AG09222. There were no clinically significant findings or trends in clinical safety laboratory tests, vital signs, QT intervals, or physical or eye examinations.

Of the 68 subjects who received Lu AG09222, 8 subjects were ADA-positive during the study, with no positive ADA tests observed before Day 84 after IMP administration (corresponding to approximately CCI Lu AG09222). Of those, only one subject was positive for ADAs at the 6-month follow up. All ADA-positive results were NAb-negative during the study, except at the 3-month follow-up, where 2 subjects were Nab-positive. None of the ADA-positive subjects had TEAEs associated with immunogenicity.

In the preliminary PK analyses, the increase in Lu AG09222 exposure appeared to be dose proportional over the full dose range and the half-life of Lu AG09222 was approximately CCI

Exposure, area under the plasma/serum concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$) and C_{max}, for the highest dose administered, CCI IV, was below the no-observed-adverse-effect-level in rats and monkeys following multiple weekly IV administration for 4 weeks. No relevant sex differences in the PK parameters were observed. The PK of Lu AG09222 CCI IV were not affected following co-administration with sumatriptan 6 mg SC compared to the results for Lu AG09222 CCI IV administered alone. Similarly, the PK of sumatriptan overall was not affected by the co-administration of Lu AG09222.

In conclusion, the preliminary safety data from this study indicate that the administration of Lu AG09222 in single IV doses of up to CCI in healthy subjects is generally safe and well tolerated. However, although this study investigated a broad range of doses, this was only as single doses and only in a limited number of subjects. Therefore, based on the profile of TEAEs in this study, adverse events related to the mechanism of action of Lu AG09222 may be expected, but the relationship between Lu AG09222 dose and the incidence of these events is uncertain.

1.2 Rationale for the Study

The rationale for this study is based on the observed nonclinical and clinical data of Lu AG09222 suggesting its potential as a safe and well-tolerated treatment to prevent migraine through blockade of PACAP signalling. Preliminary results from the FIH study support that administration of Lu AG09222 in single IV dose of up to CCI is safe and generally well tolerated in healthy men and women. The current Phase IIa study is designed to test proof-of-concept (PoC), that is, to investigate whether the inhibitory action of Lu AG09222 on the PACAP pathway can be an effective means of migraine prevention in patients with EM or CM. Further, dedicated dose-finding exploration is planned if efficacy is observed in this study.

2 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 3.

Panel 3 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments	• Primary endpoint: – Change from baseline in the number of monthly migraine days (MMDs) (Weeks 1 to 4) • Secondary endpoints: – 50% MMD response: ≥50% reduction from baseline in MMDs (Weeks 1 to 4) – Change from baseline in the number of monthly headache days (MHDs) (Weeks 1 to 4) • CCI [redacted]

Objectives	Endpoints
Primary Objective (continued)	– CCI [redacted]
[redacted]	[redacted]

Objectives	Endpoints
CCI	

Objectives	Endpoints
Safety Objective • To evaluate the safety and tolerability of Lu AG09222	**Safety Endpoints** • Adverse events • Physical examination • Absolute values and changes from baseline in clinical safety laboratory test values, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), weight, and ECGs • Potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values • Development of specific ADA including NAb • C-SSRS score

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[49]

This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled Phase IIa study designed to demonstrate PoC, that is, to investigate whether the inhibitory action of Lu AG09222 on the PACAP pathway can be an effective mechanism for migraine prevention.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[50] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

A total of 230 patients, recruited from specialist settings, are planned for randomization: 92 in the Lu AG09222 CCI group, 46 in the Lu AG09222 CCI group, and 92 in the placebo group.

The target population for this study is defined as patients diagnosed with migraine as outlined in the ICHD-3 guidelines[1], with documented evidence of migraine occurring on CCI per month prior to screening, as confirmed via prospectively collected information in the eDiary during the screening period and with documented evidence of failure of 2 to 4 different preventive migraine medications in the past 10 years. Patients with a concurrent diagnosis of MOH are allowed in the study. The aim is that approximately 30% of the randomized patients will have EM (patients with headache occurring on <15 days). This will be ensured through a cap on the number of randomized EM patients.

Once the cap (approximately 30% of the randomized patients with EM) is reached, there will be a hard stop for screening further patients with a diagnosis of EM such that:

- If the patient has a confirmed diagnosis of EM at the Screening Visit, then the patient should be considered as screen failed.

- If the patient has a confirmed diagnosis of CM at the Screening Visit but then the patient is classified as EM at the end of the screening period (based on the eDiary), then the patient should be considered as screen-failed prior to randomization.

Patients will be randomly allocated via a randomization system, using interactive response technology (IRT), to one of three treatment groups: Lu AG09222 CCI Lu AG09222 CCI or placebo, in a ratio of 2:1:2.

CCI [redacted]

Randomization will be stratified by region (Europe versus North America) CCI [redacted]

The total study duration from the Screening Visit to the Safety Follow-up Visit is approximately 16 weeks and includes a screening period (28 to 30 days), treatment period (4 weeks), and safety follow-up period (8 weeks). Patients will complete a daily headache eDiary from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit.

Patients will receive the IMP in the form of a single-dose administration at the Baseline Visit with either Lu AG09222 or placebo by IV infusion over 30 minutes (+15 minutes).

During the Baseline Visit, assessments of safety will be performed before and after the infusion. The PROs must be completed prior to infusion. Patients must complete the eDiary recording of headaches that ended prior to infusion (i.e., for headaches which are ongoing or not yet recorded in the eDiary).

Patients who withdraw prior to the Primary Outcome Visit (Week 4), except for those who withdraw their consent, will have a Withdrawal Visit as soon as possible, an Efficacy Follow-up (Phone Contact) Visit at Week 4, and a further Safety Follow-up Visit at 12 weeks after administration of the IMP (the Baseline Visit). If the Withdrawal Visit takes place at Week 4, an Efficacy Follow-up (Phone Contact) Visit at Week 4 is not required.

Safety data will be reviewed on an ongoing basis and evaluated regularly by the Lundbeck Safety Committee. In addition, an independent DMC will regularly monitor the safety data according to the *DMC Charter*.

CCI [redacted]

CCI [redacted]

3.2 Rationale for the Study Design

The study is intended to demonstrate PoC by showing efficacy and safety in patients with migraine who are eligible for preventive treatment. The study population is selected based on the substantial proportion of patients who do not respond to, or cannot tolerate, existing migraine treatments[8,9,10,11,12,13] and the need for preventive medications that are more effective and better tolerated than the current standard of care.[16] Thus, the current study will recruit patients who failed 2-4 prior preventive treatments for migraine to address a high unmet need. This target population corresponds to the patient populations recruited in recently completed migraine trials.[51,52,53]Amongst the patients with migraine, there is a proportion diagnosed with concurrent MOH.[16,54] These patients are allowed to be included in the study to investigate whether Lu AG09222 is an effective migraine preventive treatment for patients with a dual diagnosis of migraine and medication overuse headache.

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, i.e., migraine occurring CCI [redacted] and headache occurring on ≤26 days. The proposed study population comprises patients who have at least CCI [redacted] per month. CCI [redacted] he 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 randomisation, 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[17,18] for controlled studies of preventive treatment of EM and CM in adults. For migraine with aura, the patient's usual aura will only be described and diagnosed at the Screening Visit to minimise patient burden during the study. During the study, the patient will be asked about occurrence of aura with headache on a daily basis in the eDiary. Furthermore, as the first PoC study in the Lu AG09222 development program focuses on the headache phase and associated symptoms in the migraine days definition, only an aura accompanied by a minimum 30 minute-headache will count as a migraine. 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 patient 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 with a headache that is successfully treated with migraine-specific acute medication.

The current study has a classic placebo-controlled design for studies of preventive treatments in migraine, including two active doses CCI [redacted] of Lu AG09222 to help define the dose range for future dedicated dose-finding exploration. The dose selection is based on preclinical and preliminary FIH safety and PK data, as well as the target engagement data

obtained in humans. No safety signals of concern were related to the administration of CCI (the highest dose used in the FIH study) and is thus selected to maximize the chance of seeing an effect in patients with migraine. CCI [redacted]

Inclusion of a placebo group is justified since the group is representative of the best supportive care (BSC) allowing acute treatment of migraine when prior preventive treatments have not worked. Thus, the study will compare the efficacy of Lu AG09222 and BSC versus BSC alone.

The sample size for the primary endpoint was chosen based on the variation seen in the Phase III eptinezumab data[55,56] of the target population, on the expected mean change from baseline to the number of MMDs over Weeks 1 to 4, and should provide adequate power for detection of a clinically meaningful treatment effect in patients receiving the high dose of Lu AG09222. CCI [redacted]

The study treatment duration of 4 weeks is based on the CCI of Lu AG09222 as well as the FIH target engagement data and is considered an adequate period to investigate clinical efficacy. Additionally, endpoints will be evaluated at Week 12 to investigate if the relative efficacy is sustained in this population with difficult-to-treat migraine. Patients will undergo assessments related to their migraine symptoms, migraine-related disability, and impact on quality of life. The onset of the preventive effect will be explored specifically with early time points.

Furthermore, CCI [redacted]

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

In general, safety data with Lu AG09222 have not raised any clinical safety concerns at doses of up to CCI from the FIH study. However, it cannot be ruled out that the Lu AG09222 could have adverse effects that have not yet been identified. Blood sampling will be required at several time points during the study to evaluate standard safety laboratory parameters and ADAs, including NAbs. CCI [redacted]

CCI [redacted]

Safety data will be reviewed on an ongoing basis and evaluated regularly by the Lundbeck Safety Committee. In addition, an independent DMC will regularly monitor the safety data according to the *DMC Charter*. This will ensure that prompt action is taken, if needed.

Blood sampling will be required at several time points during the study to evaluate standard safety laboratory parameters, PK and PD assessments, and ADA assessments. This collection of blood samples is typical for this type of trial and does not raise any safety concerns.

4 Ethics

4.1 Ethical Rationale

This study will evaluate Lu AG09222 as a potential therapeutic candidate for a target patient population with EM or CM that is eligible for preventive treatment.

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

The randomization ratio of 2:1:2 increases the possibility that the patient will receive an active treatment.

Three treatment groups (CCI [redacted] Lu AG09222, CCI [redacted] Lu AG09222, and placebo) are considered for the current study as these have shown to be well tolerated in the FIH study and will help guide the dose selection for this target population.

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

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

In accordance with *Good Clinical Practice*,[50] qualified medical personnel at Lundbeck or the clinical contract research organization (CRO) will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Safety Committee to ensure that prompt action is taken, if needed. In addition, an independent DMC will regularly monitor the safety data according to the *DMC Charter*.

In accordance with *Good Clinical Practice*,[50] the investigator will be responsible for all study-related medical decisions.

Based on the data from 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.

The signed *Informed Consent Form* must be obtained prior to the Screening Visit if the investigator/designee needs to obtain relevant documentation from the patient's treating physician (i.e., patient's general medical and migraine history, migraine treatment history including preventive treatment failures, recent and current medication). After the information has been obtained, the patient will be invited to the site again to complete the Screening Visit.

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 8.9)
- of their right to request a copy of their personal data from the study via the investigator
- of their right to be informed by the investigator, after the study has been reported, about which treatment they received
- of their right to receive information about the study results from the investigator on the patients' own initiative; the results will be available approximately 1 year after the end of the study

The patients must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, ethics committees [ECs], or institutional review boards [IRBs]) may view their medical records. The patients must also

be informed that de-personalized copies of parts of their medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, 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*.

CCI

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[57] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck or delegate and the external organization to ensure compliance with the above-mentioned legislation.

4.4 Ethics Committee(s) and Institutional Review Board(s)

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

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

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

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

5 Study Population

5.1 Number of Patients and Countries

Planned regions: Approximately 30 sites in select countries across North America and Europe.

Planned number of screened patients (approximately):	460
Planned number of randomized patients:	230

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 at the Screening Visit (unless otherwise specified) and none of the exclusion criteria at the Screening Visit (unless otherwise specified) are eligible to participate in this study.

Inclusion Criteria

1. The patient is capable of communicating with the site personnel.
2. The patient able to read and understand the *Informed Consent Form*.
3. The patient has signed the *Informed Consent Form*.
4. The patient is an outpatient.
5. The patient has adequate venous access for administration of study drug.
6. The patient has a diagnosis of migraine as defined by ICHD-3 guidelines (section 1.1 Migraine without Aura, or 1.2 Migraine with Aura, or 1.3 Chronic Migraine)[1] confirmed at the Screening Visit.
7. The patient has a history of migraine onset at least 12 months prior to the Screening Visit.
8. The patient has a migraine onset at ≤50 years of age.
9. The patient has CCI [redacted] per month for each month within the past 3 months prior to the Screening Visit.
10. The patient fulfils the following criteria for migraine in prospectively collected information in the eDiary during the screening period:
    - Migraine occurring on CCI [redacted] and headache occurring on ≤26 days (see section 9.1.3 for *Definition of a Migraine Day* and *Headache Day*).
11. The patient has demonstrated compliance with the headache eDiary by entry of data for at least 24 of the 28 days following the Screening Visit (see section 9.1.3 for *Definition of a Compliant Day*).
12. The patient has documented evidence of treatment failure[a] (must be supported by medical record or by treating physician's confirmation specific to each treatment – see chapter 12) in the past 10 years of at least 2 to 4 (maximum) different migraine preventive medications out of the following:
    - CGRP-directed therapies (monoclonal antibodies or gepants)[b]
    - Propranolol/metoprolol
    - Topiramate
    - Amitriptyline
    - Flunarizine
    - Candesartan
    - Valproate/divalproex
    - Botulinum toxin (if documented that botulinum toxin was taken for CM)
13. The patient is aged ≥18 and ≤65 years at the Screening Visit.

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

[b] CCI [redacted]

14. The patient, if a woman, must:
    - remain sexually abstinent, when this is in line with her preferred and usual lifestyle
      OR
    - engage exclusively in same-sex relationships
      OR
    - agree to avoid becoming pregnant from the screening visit until 6 months after the administration of IMP, **AND**
    - use a highly effective contraceptive method (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly) as required by local regulation or practice if she is of childbearing potential and she has a male partner. The contraceptive method must be used from the Visit 1 until 6 months after the administration of IMP and must include one of the following: intrauterine device; contraception implant; progesterone-only pills; injectable progestogen (Depo-Provera®); combination hormonal contraceptive method (tablets, patches, or vaginal ring with both oestrogen and progestogen), **OR**
    - have had her last natural menstruation ≥12 months prior to the screening visit (confirmed by FSH level), **OR**
    - have had a hysterectomy prior to the screening visit, **OR**
    - have been surgically sterilized prior to the screening visit, **OR**
    - have a male partner who was surgically sterilized prior to the screening visit
      AND
    - not donate ova until 6 months after the administration of IMP
15. The patient, if a man, must:
    - remain sexually abstinent, when this is in line with his preferred and usual lifestyle, **OR**
    - engage exclusively in same-sex relationships
      OR
    - agree to avoid impregnating his partner from the Screening Visit until 6 months after the administration of IMP, **AND**
    - use a highly effective contraceptive method as required by local regulation or practice if his female partner is of childbearing potential. The contraceptive method must be used from the Screening Visit until 6 months after the administration of IMP and the contraceptive method to be used as an additional measure by his partner must include one of the following: intrauterine device; contraception implant; progesterone-only pills; injectable progestogen (Depo-Provera®); combination hormonal contraceptive method (tablets, patches, or vaginal ring with both oestrogen and progestogen), **OR**
    - have been surgically sterilized prior to the Screening Visit, **OR**
    - have a partner who had her last natural menstruation ≥24 months prior to the Screening Visit, **OR**
    - have a partner who had a hysterectomy prior to the Screening Visit, **OR**
    - have a partner who was surgically sterilized prior to the Screening Visit
      AND

- not donate sperm until ≥6 months after the administration of IMP

16. The patient has provided a signed optional *subset-specific Informed Consent Form* or an optional biobank *Informed Consent Form*, if applicable.

Exclusion Criteria

1. The patient has previously been enrolled in this study.
2. The patient has participated in a clinical study <30 days prior to the Screening Visit.
3. The patient has been previously dosed with an anti-PACAP ligand -targeting antibody.
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 known hypersensitivity or intolerance to any of the IMPs or their excipients.
7. The patient has a history of severe drug allergy or hypersensitivity. Hay fever is allowed unless it is active.
8. The patient has confounding and clinically significant pain syndromes (for example, fibromyalgia, chronic low back pain, complex regional pain syndrome).
9. The patient has a diagnosis of acute or active temporomandibular disorder.
10. The patient has a history or diagnosis of chronic tension-type headache, cluster headache, headache attributed to trauma or injury to the head and/or neck, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua, primary thunderclap headache, primary stabbing headache, nummular headache, new daily persistent headache, hypnic headache, trigeminal neuralgia, or unusual migraine subtypes such as hemiplegic migraine (sporadic and familial), recurrent painful ophthalmoplegic neuropathy, migraine with brainstem aura, or migraine with neurological accompaniments that are not typical of migraine aura (diplopia, altered consciousness, or long duration).
11. The patient has a lifetime history of psychosis, bipolar mania, or dementia. Patients with other psychiatric conditions whose symptoms are not controlled or who have not been adequately treated for a minimum of 6 months prior to screening are also excluded.
12. The patient has a current diagnosis or history of substance or alcohol use disorder (DSM-5® criteria) <24 months prior to the Screening Visit or substance use deemed significant by the investigator (excluding nicotine or caffeine).
13. The patient has reported current use of, or has tested positive for, drugs of abuse (cocaine, amphetamines, phencyclidine, propoxyphene).
14. 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.
15. 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.

16. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin or adequately treated cervical intraepithelial neoplasia, that has not been in remission for >5 years prior to the dose of IMP.
17. The patient has or has had one or more of the following conditions that is/are considered clinically relevant in the context of the study: other neurological, pulmonary, hepatic, endocrinological, gastrointestinal, haematological, infectious, immunological (including autoimmune), rheumatological, or ocular disorders.
18. 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).
19. The patient has had surgery or trauma with significant blood loss <3 months prior to the dose of IMP.
20. The patient has donated blood <3 months prior to the dose of IMP.
21. The patient takes or has taken recent or concomitant medication that is disallowed or has not met the restrictions for a medication that is 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.
22. The patient has one or more clinically significant out-of-range vital signs at the Screening Visit.
23. The patient has orthostatic hypotension, defined as a decrease in systolic blood pressure ≥20 mmHg from supine to standing, at the Screening Visit or at the Baseline Visit.
24. The patient has a body mass index (BMI) >30 kg/m^2 at the Screening Visit.
25. The patient has previously tested positive for human immunodeficiency virus (HIV).
26. The patient has tested positive for hepatitis C virus antibody (anti-HCV) or has been tested for hepatitis B serology and is confirmed to have acute or chronic infection (refer to Appendix III for interpretation).
27. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase or aspartate aminotransferase value >2 times the upper limit of the reference range
28. The patient has, at the Screening Visit, an abnormal electrocardiogram (ECG) that is, in the investigator's opinion, clinically significant.
29. The patient has a heart rate-corrected QT interval (QTc) >450 ms (Fridericia's correction) at the Screening Visit, as calculated by the central reading vendor and evaluated by the investigator. The ECG may be repeated if any of the values are out of range or abnormal.
30. The patient is, at the Screening Visit or Baseline Visit, at significant risk of suicide (defined, using the C-SSRS), as the patient answering: "yes" to suicidal ideation questions 4 or 5 within the past 12 months or answering: "yes" to suicidal behaviour within the past 12 months).

31. 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.
32. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

5.4 Withdrawal Criteria

A patient must be withdrawn from the study if:

- The patient withdraws their consent (defined as a patient who explicitly takes back their consent); section 8.9 states how the patient's data will be handled.
- The patient has been randomized in error and has not received IMP.
- The patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient]).
- The patient is at significant risk of suicide (defined as answering "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS at any time during the study.
- 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.
- 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.
- Any site personnel break the randomization code for that patient.
- The patient becomes pregnant.

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

Patients will be randomly allocated via a centralized randomization system to one of three treatment groups: Lu AG09222 CCI Lu AG09222 CCI or placebo, in a ratio of 2:1:2.

The patient will receive IMP at the Baseline Visit with either Lu AG09222 CCI Lu AG09222 CCI or placebo by IV infusion.

6.2 IMP, Formulation and Strength

The IMP supplied by Lundbeck in this study is:

- Lu AG09222 solution for injection/infusion CCI

Patients allocated to the [redacted] Lu AG09222 treatment group will be dispensed 1 vial of Lu AG09222 solution for injection/infusion [redacted] added to 0.9% normal saline (total volume of [redacted] IV.

Patients allocated to the [redacted] Lu AG09222 treatment group will be dispensed 8 vials of Lu AG09222 solution for injection/infusion [redacted] (of which [redacted] will be used) added to 0.9% normal saline (total volume of [redacted] IV.

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

The pharmacist or designee responsible for receiving, storing, preparing, and dispensing Lu AG09222 and placebo IV infusions will be unblinded and will not be responsible for other aspects of the clinical study where blinding is necessary.

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

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

6.3 Manufacturing, Packaging, Labelling, and Storage of IMP(s)

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

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

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

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

The IMP will be identified using a unique medication number.

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

6.4 Method of Assigning Patients to Treatment

The IRT will be used in this study. Each patient will be assigned a screening number by the IRT, and that number will be used to identify the patient throughout the study. Randomization of the patient will be performed in the IRT. The IRT allocates the patient to a treatment group and assigns the patient a randomization number in accordance with the specifications from Biostatistics, H. Lundbeck A/S.

Randomization will be stratified by region (North America versus Europe) [redacted]

6.5 IMP Accountability

IMP accountability is documented in the IRT by the unblinded clinical research associate (CRA).

The investigator and the pharmacist must agree to only dispense IMP to patients enrolled in the study. The unblinded pharmacist must maintain an adequate record of the receipt and distribution of the IMP. 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, the investigator or the pharmacist (if applicable) and the DMC will have access to the unblinded information for the double-blind treatment for each patient. Access to these details will be via IRT.

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

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

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

Details of all concomitant medication (prescription and over the counter), herbal remedies, non-pharmacological interventions, vitamin and mineral supplements for the treatment of migraine taken and substance use <3 months prior to the Screening Visit must be recorded in the electronic case report form (eCRF) at the first visit. Any changes (including reason for changes) in concomitant medication and non-pharmacological interventions must be recorded at each subsequent visit. Any changes in substance use must be collected at selected visits until the Safety Follow-up/Withdrawal Visit.

Vaccinations (including COVID-19 vaccines) are allowed provided the vaccinations have been completed for at least 14 days prior to the Screening Visit. Vaccinations during the study are allowed providing the vaccination is received at least 3 days after the IMP administration. The vaccinations, including brand names, if used during the study must be reported as concomitant medications.

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

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

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

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.

Appropriate risk assessment and mitigations will be done in case of restrictions due to COVID-19, which will be described in detail in a separate COVID-19 mitigation plan.

The Screening Visit (Visit 1) is performed 28 to 30 days before the Baseline Visit (Visit 2). At the Baseline Visit (Visit 2), the IMP is administered. The Primary Outcome Visit (Visit 4)

is performed 4 weeks after the Baseline Visit. A Safety Follow-up Visit (Visit 6) is performed 8 weeks after the Primary Outcome Visit.

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

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

Patients will record eDiary headache data on a daily basis from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit. At each visit, a compliance check of eDiary (based on eDiary reporting) 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. See section 9.2.1.2 for further details on eDiary.

Patients will complete the PROs in alignment with scheduled visit dates. PROs scheduled at the Baseline Visit (Visit 2) must be completed in the clinic at the visit date and before the infusion. PROs scheduled in alignment with all other visits can be completed on the day or within 3 days prior to the scheduled visit date. See section 9.2.1 for further details on PROs.

Patients who withdraw prior to the Primary Outcome Visit (Week 4), except for those who withdraw their consent, will have a Withdrawal Visit as soon as possible, an Efficacy Follow-up (Phone Contact) Visit at Week 4, and a further Safety Follow-up Visit at 12 weeks after administration of the IMP (the Baseline Visit). If the Withdrawal Visit takes place at Week 4, an Efficacy Follow-up (Phone Contact) Visit at Week 4 is not required (see section 8.10).

Visit 3, Visit 4 (Primary Outcome Visit), Visit 5, and Withdrawal Visit can be conducted as a clinic visit to the site by the patient or can be provided as a home visit by a healthcare provider/study site staff with or without a televisit through teleconferencing. Before these visits are conducted, patients will have the option to choose the types of visits to be conducted and these are allowed to be changed during the study. The type of visits conducted must be recorded in the eCRF. Further information on the type of visits will be provided in the *Site Guide for Off-Site Nursing Services and TeleVisit Solutions Site Reference Guide*.

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 a visit to the site. Signed informed consent must be in place before any study-related assessments are performed (including collection of relevant documentation from the patient's treating physician) and may be obtained prior to the Screening Visit. See section 9.1 for further details on screening assessments and chapter 12 for further details on relevant documentation from the treating physician.

CCI [redacted]

At the Screening Visit, the patient must be assisted with the provisioning of the eDiary and PROs and must be trained in their use and compliance requirements. Details will be provided in a separate *eDiary and PRO site information guide* (see section 9.2.1.2 for further details on the eDiary and section 9.2.1 for further details on PROs).

In exceptional cases, the screening period (the visit interval between the Screening and Baseline Visits) may be extended with approval from the sponsor provided the Lundbeck medical expert (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 to advise if the patient appears eligible or not 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 only allowed for patients with a *complete* Screening Visit and who do not fulfil the following:

- The required duration of a washout period for a medication that is disallowed prior to screening, or
- A stable usage period for a medication that is allowed with restrictions prior to screening.

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

The patient must already have either started the washout prior to screening or be on the allowed dosage as part of their standard clinical care. Washout or change in dosage may not be done specifically for inclusion into this study.

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

The new Screening Visit must be conducted as a visit to the site. At the new Screening Visit, the patient must sign a new *Informed Consent Form*. At the new Screening Visit, the patient will be assigned a new screening number. A re-screened patient must have a *completely* new Screening Visit, and all the eligibility criteria must be re-assessed at the new Screening Visit.

The following information will be recorded in the eCRF at the new Screening Visit:

- that the patient has previously been screened for the study
- that re-screening has been authorized by the sponsor's medical expert (or the CRO's medical monitor)
- the screening number that was assigned to the patient at the original Screening Visit

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

A patient may only be re-screened once.

8.3 Baseline + IMP Visit (Visit 2)

The Baseline Visit must be conducted as a visit to the site and will occur 28 to 30 days after the Screening Visit. In exceptional cases, the visit interval between the Screening and Baseline Visits may be extended with consent from the Lundbeck medical expert, provided the Lundbeck medical expert accepts the rationale provided for the extension.

Prior to the Baseline Visit, study-specific eligibility must be reviewed by the CRO's medical monitor 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 the 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 the eDiary recording of headaches that ended prior to infusion (i.e., for headaches which are ongoing or not yet recorded in the eDiary). See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the Baseline Visit must be completed in the clinic and prior to infusion. CCI [redacted] 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. Clinician-reported outcomes (ClinROs; CCI [redacted] and C-SSRS) must be administered by the authorized rater after the PROs are completed and prior to infusion. See section 9.2.1 for further details on PROs.

At the Baseline Visit, the patients will receive a dose of IMP. See section 6.2 and *Infusion Guidelines* for further instructions on procedures associated with administering the IV IMP.

Prior to IMP infusion:

- Patients must complete the PROs. PROs can be completed at the patient's convenience before or after the pre-infusion blood and urine sampling.
- The following assessments must be conducted/collected: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), concomitant medications and substances (prescription and non-prescription), non-pharmacological interventions, adverse events, physical and neurological examinations, ECG, blood sampling (for clinical safety laboratory tests, CCI [redacted] ADA including NAb, and optional CCI [redacted] and urine sampling (for clinical safety laboratory and pregnancy tests), CCI [redacted] and C-SSRS. Vital signs must be assessed prior to blood sampling.

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

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

- Patients must be monitored for at least 2 hours.
- The following assessments must be conducted: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), IRRs, and adverse events. IRRs must be assessed after the adverse event collection.
- A blood sample for CCI [redacted] quantification must be taken immediately after end of infusion (EOI) and 2 hours after EOI. Vital signs must be assessed prior to blood sampling.
- Patients will be requested to stay longer should the investigator or designee determine this is clinically warranted.
- After the infusion, the patients will be under observation, but not confined to bed, unless the investigator 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 Visit 3

The Week 2 Visit can be conducted as a visit to the site or a home visit with or without a televisit. See section 8.1 for further details on the types of visits. The Week 2 Visit should be planned to maintain the visit schedule relative to the Baseline Visit.

A compliance check of the eDiary will be conducted. See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the scheduled visit can be completed on the day or within 3 days prior to the scheduled visit date. CCI [redacted] 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. It is preferred to take the CCI [redacted] in the

morning, if possible. This may put the CCI out of the order in relation to the other assessments when performed in the morning. See section 9.2.1 for further details on PROs.

Blood sampling will be taken for CCI and ADA (including NAb) quantification. Relevant assessments for safety will be conducted including blood and urine sampling for clinical safety laboratory tests and C-SSRS. C-SSRS must be administered by the authorized rater after the PROs are completed. Adverse events, concomitant medication (prescription and non-prescription) and non-pharmacological interventions will be collected.

8.5 Primary Outcome Visit (Visit 4)

The Primary Outcome Visit can be conducted as a visit to the site or a home visit with or without a televisit. See section 8.1 for further details on the types of visits. The Primary Outcome Visit should be planned to maintain the visit schedule relative to the Baseline Visit.

A compliance check of the eDiary will be conducted. See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the Primary Outcome Visit can be completed on the day or within 3 days prior to the scheduled visit date. CCI t 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. It is preferred to take the CCI in the morning, if possible. This may put the CCI out of the order in relation to the other assessments when performed in the morning. See section 9.2.1 for further details on PROs. CCI must be administered by the authorized rater after the PROs are completed. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

Blood sampling will be taken for CCI ADA (including NAb), and optional CCI Relevant assessments for safety will be conducted including blood and urine sampling for clinical safety laboratory tests, pregnancy test, and C-SSRS. C-SSRS must be administered by the authorized rater after the PROs are completed.

8.6 Visit 5

The Week 8 Visit can be conducted as a visit to the site or a home visit with or without a televisit. See section 8.1 for further details on the types of visits. The Week 8 Visit should be planned to maintain the visit schedule relative to the Baseline Visit.

A compliance check of the eDiary will be conducted. See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the scheduled visit can be completed on the day or within 3 days prior to the scheduled visit. CCI

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. It is preferred to take the CCI in the morning, if possible. This may put the CCI out of the order in relation to the other assessments when performed in the morning. See section 9.2.1 for further details on PROs. CCI must be administered by the authorized rater after the PROs are completed. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

Blood sampling will be taken for CCI and ADA (including NAb) quantification. Relevant assessments for safety will be conducted including blood and urine sampling for clinical safety laboratory tests and C-SSRS. C-SSRS must be administered by the authorized rater after the PROs are completed.

8.7 Safety Follow-up Visit (Visit 6)

Patients will attend the Safety Follow-up Visit which must be conducted 8 weeks after the Primary Outcome Visit (i.e., 12 weeks after administration of IMP). The Safety Follow-up Visit must be conducted as a visit to the site. 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 treatment period. Relevant assessments for safety will be conducted including blood and urine sampling for clinical safety laboratory tests, pregnancy test, and C-SSRS. C-SSRS must be administered by the authorized rater after the PROs are completed. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

The eDiary closeout will take place at the Safety Follow-up Visit while the patient is at the site. Details will be provided in a separate *eDiary and PRO training material*. See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the scheduled on-site visit can be completed on the day or within 3 days prior to the scheduled on-site visit. CCI 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. It is preferred to take the CCI in the morning, if possible. This may put the CCI out of the order in relation to the other assessments when performed in the morning. See section 9.2.1 for further details on PROs. CCI must be administered by the authorized rater after the PROs are completed.

Blood sampling will be taken for CCI and ADA (including NAb) quantification.

A proportion of patients who complete the Safety Follow-up Visit (Week 12) will be asked to provide additional blood samples for post-study immunogenicity testing at 12-week intervals (potentially up to 12 months relative to the infusion date). The number of patients from

whom these samples will be collected will be decided during the study in consultation with the sponsor.

For patients with a clinically significant out-of-range clinical safety laboratory test value at the Safety Follow-up Visit, further safety follow-up should be scheduled in accordance with usual clinical practice until the value normalizes or stabilizes or a diagnosis or reasonable explanation has been established. Any further safety follow-up after the last protocol-specified contact with the patient will be recorded in the patient's medical records and not in the eCRF; see section 10.5 for details.

For adverse events that were ongoing at the end of the treatment period 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 Visit, the *Ongoing Adverse Event* checkbox on the *Adverse Event Form* must be ticked. SAEs must be followed until resolution or the outcome is known.

Patients who withdraw from the study prior to the Primary Outcome Visit, except for those who withdraw their consent, will have a Withdrawal Visit as soon as possible and a further Safety Follow-up Visit at 12 weeks after administration of IMP (the Baseline Visit). At the Safety Follow-up Visit, withdrawn patients will not be required to complete the efficacy assessments. Details will be provided in a separate *eDiary* and *PRO training material*.

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

CCI [redacted]

8.8 Unscheduled Visit

An unscheduled visit may occur throughout this study if needed preferably as a site visit (depending on the assessments required). At these visits, clinical safety laboratory tests, ECG, vital signs, physical or neurological examinations can be performed. In case of any additional tests performed that are not covered by the existing tests specified in the protocol and the eCRF, the results can be reported in connection with an AE reporting (see chapter 10) or documented in the medical notes, as applicable. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

8.9 Withdrawal Visit

Patients who withdraw from the study prior to the Primary Outcome Visit (Week 4) will have a Withdrawal Visit, if possible, which can be conducted as a visit to the site or a home visit with or without a televisit. The visit must be scheduled as soon as possible after withdrawal.

At the Withdrawal Visit, a compliance check of the eDiary will be conducted. The eDiary assessments should continue on a daily basis until Week 4. Thus, if the patient withdraws between Week 3 and Week 4, then the Withdrawal Visit should be scheduled at Week 4 to align with the eDiary closeout. If the Withdrawal Visit takes place during the treatment period and prior to Week 3, then the eDiary assessments should continue on a daily basis until Week 4 and the patient will be contacted via telephone for an Efficacy Follow-up Visit (phone contact) at Week 4 for the eDiary closeout (see section 8.10). Details will be provided in a separate *eDiary and PRO training material*. See section 9.2.1.2 for further details on the eDiary.

PROs which are scheduled in alignment with the Withdrawal Visit can be completed on the day or within 3 days prior to the scheduled visit date. CCI [redacted] t 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. It is preferred to take the CCI [redacted] in the morning, if possible. This may put the CCI [redacted] out of the order in relation to the other assessments when performed in the morning. See section 9.2.1 for further details on PROs. CCI [redacted] must be administered by the authorized rater after the PROs are completed.

Blood sampling will be taken for CCI [redacted] and ADA (including NAb) quantification, and optional CCI [redacted] Relevant assessments for safety will be conducted including blood and urine sampling for clinical safety laboratory tests and C-SSRS. C-SSRS must be administered by the authorized rater after the PROs are completed. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

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

The reason for withdrawal must be recorded in the eCRF.

For a patient who withdraws consent:

- If the patient withdraws consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including that visit will be used.
- If the patient withdraws consent during a telephone conversation, the investigator will ask the patient if 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.

The withdrawal visit does not apply if a patient withdraws during the safety follow-up period (for whatever reason). Then 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.

8.10 Efficacy Follow-up Visit (Telephone Contact)

The Efficacy Follow-up Visit is conducted as a telephone contact at Week 4 and applies to patients who withdraw from the study during the treatment period and prior to Week 3, except for those who withdraw their consent.

If the Withdrawal Visit takes place during the treatment period and prior to Week 3, then the eDiary assessments should continue on a daily basis until the Efficacy Follow-up Visit (Week 4).

At the Efficacy Follow-up Visit, a compliance check of the eDiary will be conducted. The eDiary closeout will take place at the Efficacy Follow-up Visit. Patients will not be required to complete the PRO assessments. Details will be provided in a separate *eDiary and PRO training material*. Adverse events, concomitant medication (prescription and non-prescription), and non-pharmacological interventions will be collected.

If the Withdrawal Visit takes place at Week 4, an Efficacy Follow-up (telephone contact) Visit at Week 4 is not required and the eDiary closeout must take place at the Withdrawal Visit (see section 8.9).

8.11 End-of-study Definition

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

9 Assessments

9.1 Screening and Baseline Procedures and Assessments

9.1.1 Demographics and Baseline Characteristics

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

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

- Demographics (age, sex, race)
- Migraine history (including diagnosis of migraine and MOH) *

- Relevant history (social, medical, psychiatric, neurological)
- Prior migraine treatment history for review and documentation of previous preventive medication use including treatment failures (see below for definition) ** within the 10 years prior to the Screening Visit (see chapter 12 for adequate required documentation)
- Other recent medication (including acute migraine medications)
- Substance use (alcohol, tobacco, caffeine, marijuana consumption) ***
- Height without shoes
- Blood sample for screening (e.g., β-hCG [beta-human chorionic gonadotropin], FSH, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], and anti-HCV) and other clinical safety laboratory tests (as listed in Panel 5)
- Urine sample for screening (drug and alcohol screen) and other clinical safety laboratory tests (as listed in Panel 5)
- Signs and symptoms present at the Screening and/or Baseline Visits (before IMP administration)
- CCI [redacted]
- Vital signs (including blood pressure, pulse, respiratory rate, and body temperature), weight without shoes, ECGs
- Physical and neurological examinations must be performed prior to the infusion.
- C-SSRS to systematically assess suicidal ideation and behaviour of patients for safety (see section 9.5.7)

*Patients with a concurrent diagnosis of MOH are allowed to be included in the study. At the Screening Visit, the investigator must confirm whether or not the patient has a concurrent diagnosis of MOH.

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

*** Substance use <3 months prior to screening will be collected at the Screening Visit. Substance use during the screening period will be collected at the Baseline Visit. Substance use throughout the study (including any changes in substance use) will be collected at select visits until the Safety Follow-up/Withdrawal Visit.

9.1.2 Diagnostic Assessments

The ICHD-3 guidelines[1] section 1.1 Migraine without Aura, or 1.2 Migraine with Aura, or 1.3 Chronic Migraine are the diagnostic criteria to be used when assessing patient eligibility (see Panel 4).

Panel 4 ICHD-3 Guidelines for Migraine[1]

1.1 Migraine without Aura	1.2 Migraine with Aura
A. At least five attacks fulfilling criteria B–D B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated) C. Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis.	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5–60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis.

1.3 Chronic Migraine

A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without Aura and/or criteria B and C for 1.2 Migraine with Aura

C. On ≥8 days/month for >3 months, fulfilling any of the following:
1. criteria C and D for 1.1 Migraine without Aura
2. criteria B and C for 1.2 Migraine with Aura
3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.

ICHD-3 = International Classification of Headache Disorders Third Edition.

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, i.e., migraine occurring on CCI and headache occurring on ≤26 days. Prior to randomisation, the investigator will review the data in the *eDiary Eligibility Report* to determine if eligibility criteria are fulfilled.

Definition of a Migraine Day: The definition is based on the IHS guidelines[17,18] for controlled studies of preventive treatment of CM and EM in adults. A migraine day is defined as a day with a headache that:

- lasts ≥4 hours and meets ICHD-3 criteria C and D for migraine without aura (1.1),
- or lasts ≥30 minutes and where the patient had an aura with the headache (migraine with aura*),
- or lasts ≥30 minutes and meets two of the three ICHD-3 criteria B (without the condition on 72 hours), C and D for migraine without aura (1.1) (probable migraine**),
- or 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 on a daily basis for each headache day, and for each headache day it will be determined whether 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.[17]

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:

CCI [redacted]

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.

CCI [redacted]

CCI [redacted]

Definition of a 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 patient records daily symptoms, or
- headache diary is completed: confirming patient does not have any new headache to report.

9.1.4 Drug and Alcohol Screen

A urine drug and alcohol screen will be performed. If the patient has tested positive for drugs of abuse (cocaine, amphetamines, phencyclidine, propoxyphene), then the patient should be excluded. Note: Positive results for opiates, cannabinoids, and barbiturates should not be a reason for exclusion.

9.2 Efficacy Assessments

Efficacy assessments include the eDiary to record daily headache data, CCI [redacted]

Patients will record eDiary headache data on a daily basis from the time of screening until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit.

CCI [redacted]

PROs which are scheduled in alignment with a visit can be completed on the day or within 3 days prior to the scheduled visit date. On the Baseline Visit day, patients must complete the PROs at the visit date and prior to infusion (see Panel 2).

9.2.1 Clinical Outcome Assessments

9.2.1.1 Use of Clinical Outcome Assessment Tools

The clinical outcome assessment (COA) tools include the eDiary and PROs, and guidance will be given on how to complete them to the patients by designated site staff (see section 9.2.1.12). Detailed instructions will be provided to the site in a separate *eDiary* and *PRO site information guide*. Site staff will be given access to review the eDiary data.

CCI [redacted]

The COA tools will be administered in the local language. Only linguistically validated translated COAs provided by Lundbeck will be used in this study.

The following COA tools will be used for efficacy assessments:

- eDiary – to assess daily headache and migraine variables, i.e., the number of hours with headache, presence of associated symptoms, and use of acute migraine medications start and stop dates, and headache severity.
- CCI [redacted]

9.2.1.2 eDiary

Patients will complete a daily headache eDiary, from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit, that consists of applications and reports that will be used to derive the migraine and headache endpoints. The eDiary will be distributed to each patient at the Screening Visit after patient training on eDiary use. The eDiary data from the 28 days following the Screening Visit will be used to determine eligibility criteria, baseline migraine and headache values, and eDiary compliance. See section 9.1.3 for definition of a Migraine Day, Headache Day and Compliant Day during the Screening Period. Ongoing evaluation of eDiary compliance will be performed by the study site based on eDiary reports. 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. The patient will also receive training on the questions which will be asked in the eDiary. Access to training material will be available throughout the study. Patients will be instructed to complete the eDiary on a daily basis, from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit. During the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit, the eDiary closeout must be performed. Details will be provided in a separate *eDiary site information guide*.

The content of the headache diary is developed on key symptoms and characteristics as mentioned in the definition of migraine (see section 9.1.2). 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 training material*.

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 randomised. 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 and for the eligibility assessment of:

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

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

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

On each day during the study until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit, the patient will be asked to record eDiary data for the day.

Site staff will be given access to review the eDiary data. Compliance data (based on eDiary reporting) will be made available throughout the study to site staff for review on a regular basis. At each visit, a compliance check of the 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.

CCI [redacted]

CCI

[redacted]

- CCI [redacted]

[redacted]

9.2.1.12 COA Tool Training

The COA tools CCI [redacted] are PROs. Therefore, designated site staff will receive guidance on good standards in completion of the COAs in order to adequately train the patients on completion of the eDiary and PROs.

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

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

CCI [redacted] The rater should be a clinician (Medical Doctor). Any exceptions must be discussed and approved by Lundbeck and/or its designee. For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study.

Rater training and certification will be conducted by the CRO as agreed with the sponsor. Raters will complete their designated training curriculum based on their initial qualification status and assigned role. Only raters who qualify on a study-specific Rater Certification Programme will be authorized to administer the CCI [redacted] 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 CCI [redacted]

9.3 Pharmacokinetic Assessments

CCI [redacted]

9.4 Pharmacodynamic Assessments

CCI [redacted]

[c] CCI [redacted] will be analysed as part of the Clinical Safety Laboratory Panel.

[d] CCI [redacted]

9.5 Safety Assessments

9.5.1 Adverse Events

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

See chapter 10 for further information on adverse events.

9.5.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 5.

Panel 5 Clinical Safety Laboratory Tests

<table>
<tr>
<td rowspan="2">Haematology
B-haemoglobin
B-erythrocyte count
B-total leucocyte count
B-neutrophils[a]
B-eosinophils[a]
B-basophils[a]
B-lymphocytes[a]
B-monocytes[a]
B-thrombocyte count</td>
<td>Liver[b]
S-total bilirubin
S-alkaline phosphatase
S-alanine aminotransferase
S-aspartate aminotransferase
S-gamma-glutamyl transferase</td>
<td>Serology[c,i]
S-HBsAg
S-anti-HCV
S-anti-HBs
S-anti-HBc</td>
</tr>
<tr>
<td>Other
S-creatine phosphokinase
S-cardiac troponins (TnT, TnI)</td>
<td>Infection
S-C-reactive protein</td>
</tr>
<tr>
<td>Electrolytes[b]
S-sodium
S-potassium</td>
<td>Kidney[b]
S-creatinine
B/S-urea nitrogen</td>
<td>Urine[g]
U-protein (dipstick)
U-glucose (dipstick)
U-blood (dipstick)</td>
</tr>
<tr>
<td>Endocrine and Metabolic[b]
S-albumin
S-glucose[d]
B-HbA1c
S-TSH[c,h]</td>
<td>Lipids[b,d]
S-low-density lipoprotein
S-high-density lipoprotein
S-triglycerides
S-cholesterol (total)</td>
<td>Pregnancy[e] and Menopause[f]
S-β-hCG[e]
U-pregnancy dipstick[e]
S-FSH[c,f]</td>
</tr>
<tr>
<td colspan="3">anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; anti-HCV = hepatitis C virus antibody; B = blood; β-hCG = beta-human chorionic gonadotropin; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; S = serum; TSH = thyroid-stimulating hormone; U = urine</td>
</tr>
</table>

a Count and % of total leucocytes.

b Clinical chemistry.

c Performed at the Screening Visit only.
d Fasting (i.e., 6 hours prior to sample collection), when possible.
e Only for women of childbearing potential. Pregnancy test at the Screening Visit and the Safety Follow-up Visit is to be conducted using serum β-hCG. At Visit 2, Visit 4 and Withdrawal Visit, urine pregnancy testing will be performed, and, in case of a positive finding, further confirmatory testing will be performed via serum β-hCG.
f Only for women of non-childbearing potential who have had her last natural menstruation ≥12 months prior to the Screening Visit.
g If urine dipstick is positive, a urine microscopic panel will be conducted.
h In case of abnormal TSH, reflex testing of triiodothyronine (T3) and thyroxine (T4) will be conducted.
i In case of positive or indeterminate results, confirmatory testing will be performed including viral load.

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

The blood samples will be analysed at the central laboratory.

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). A patient with a value that is out of range at the Primary Outcome or Withdrawal Visit and considered clinically significant must be followed for up to 12 weeks after the out-of-range value occurred or until the value normalizes or stabilizes or a diagnosis or reasonable explanation has been established. Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical records.

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*. The central laboratory will be notified by the sponsor when the biological samples may be destroyed.

9.5.3 Vital Signs

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

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

Pulse and blood pressure will be measured using a standard digital meter. Pulse rate and blood pressure will be measured in the following order: supine and standing after the patient has rested in each position for at least 5 minutes.

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

Body temperature will be measured by an ear thermometer.

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

9.5.4 Height and Weight

The patient's height will be measured.

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

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

9.5.5 Electrocardiograms

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

The results from the central ECG laboratory will include the 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.

All Abnormal (both "Abnormal Not Clinically Significant ECGs" and "Abnormal Clinically Significant ECGs") must be described in words with a diagnosis or value (e.g., Second-degree AV-Block type Wenckebach) in the eCRF.

Any abnormal ECG result or out-of-range ECG parameter value and judged "Abnormal Clinically Significant ECGs" by the investigator must also be recorded as an adverse event on an *Adverse Event Form*.

9.5.6 Physical and Neurological Examinations

For the Baseline Visit, the examinations are to be conducted prior to the infusion.

The investigator may appoint a designee to be primarily responsible for performing the physical and neurological examinations, such as a physician assistant or nurse practitioner (as applicable), provided this is permitted according to local regulations and documented on the

site delegation log. The investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all the examinations.

The physical examination (including height at the Screening Visit only) must, at a minimum, include an examination of appearance, extremities, skin (including signs of purpura and neurological assessments for any new onset of paraesthesia or dysaesthesia), head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen, genito-urinary system, and musculoskeletal system. Note for signs of purpura, or examination of paraesthesia, dysaesthesia, or genito-urinary system:

- Self-reported symptoms are sufficient for signs of purpura in the intimate areas (i.e., genito-urinary or breast area). If the patient reports any symptoms, he/she must have an objective examination by a physician.
- Self-reported symptoms are sufficient for the examination of paraesthesia and dysaesthesia (no need for objective examination).
- For the genito-urinary system, a full gynaecological examination should only be performed if warranted by symptoms or medical history.

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*.

9.5.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is a ClinRO. The C-SSRS is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study.[58] The C-SSRS has 5 questions addressing suicidal ideation, five sub-questions assessing the intensity of ideation, and four questions addressing suicidal behaviour. For this study, the following versions of the scale are used: the "Baseline/Screening" version will be used at the Screening Visit and the "Since last visit" version will be used for all subsequent visits. It takes approximately 5 minutes to administer and rate the C-SSRS.

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

The C-SSRS should only be administered by a rater who has adequate experience with clinical studies in CNS indications. The rater should be a clinician, such as a neurologist, geriatrician, psychiatrist, or (neuro-) psychologist involved in clinical practice or regularly evaluating patients. Any exceptions must be discussed and approved by Lundbeck and/or its designee. For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study.

For a rater to be allowed to administer the C-SSRS, the rater must complete the training by Dr. Kelly Posner's group (at Columbia University) and the training assigned by the CRO before the start of study. Raters will complete their designated training curriculum based on

their initial qualification status and assigned role. Only raters who qualify on a 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.

The C-SSRS data at the Screening and Baseline Visit will be used to determine eligibility criteria. If the patient answers "yes" to suicidal ideation questions 4 or 5 within the past 12 months, or answers "yes" to suicidal behaviour within the past 12 months on the C-SSRS at the Screening Visit or Baseline Visit then the patient is not eligible. Any patient found to be ineligible will not be randomized.

If the patient answers "yes" to suicidal ideation questions 4 or 5, or answers "yes" to suicidal behaviour on the C-SSRS at the Safety Follow-up Visit, then the patient must be followed in accordance with usual clinical practice. The follow-up will be documented in the patient's medical records.

9.5.8 Anti-drug Antibody Including Neutralizing Antibody Assessments

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

A proportion of patients who complete the Safety Follow-up Visit (Week 12) will be asked to provide additional blood samples for post-study immunogenicity testing at 12-week intervals (potentially up to 12 months relative to the infusion date). The number of patients from whom these samples will be collected will be decided during the study in consultation with the sponsor. The results may be reported separately from the Clinical Study Report.

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

The samples will be analysed using a validated bioanalytical method by a bioanalytical laboratory under the responsibility of the sponsor. Samples from patients who receive active treatment will be analysed for ADA. Samples from patients who receive placebo will not be analysed. The analysis method will be defined in a bioanalytical protocol and will be reported in a bioanalytical report.

9.6 Other Assessments

CCI [redacted]

CCI

[redacted]

fallback form to Fax: +45 36 30 99 67 or email: ICSRquery@lundbeck.com within 24 hours after the case has been received. All adverse events reported to site in connection to CCI [redacted]

[redacted]

9.7 Biobanking

CCI [redacted]

[redacted]

CCI [redacted]

9.8 Order of Assessments

At the Screening Visit:

- Blood and urine sampling for clinical safety laboratory tests must be scheduled and results reviewed prior to the Baseline Visit.
- At the Screening Visit the "Baseline/Screening" version of the C-SSRS must be used. At each following visit, the "Since last visit" version of the C-SSRS must be used.

PROs:

- PROs scheduled in alignment with a visit (except the Baseline Visit) can be completed on the day or within 3 days prior to the scheduled visit date (see Panel 2).
- CCI [redacted]
- 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 Visit **prior** to infusion:

- Patients must complete recording of headaches which ended prior to infusion (i.e., for headaches which are ongoing or not yet recorded in the eDiary).
- Patients must complete the PROs. PROs can be completed at the patient's convenience before or after the pre-infusion blood and urine sampling.
- The following assessments must be conducted: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), concomitant medications, non-pharmacological interventions, adverse events, physical and neurological examination, ECG, blood sampling (for clinical safety laboratory tests, CCI [redacted] ADA including NAb, and optional CCI [redacted], and urine sampling (for clinical safety laboratory and pregnancy tests), CCI [redacted] and C-SSRS administration. Vital signs must be assessed prior to blood sampling.
- See section 8.3 for procedures preceding IMP administration.

At the Baseline Visit **during** infusion:

- IRRs must be checked as part of the overall adverse event collection. IRRs must be assessed after the adverse event collection.

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

- The following assessments must be conducted: vital signs (including blood pressure, pulse, respiratory rate, and body temperature), IRRs, and adverse events. IRRs must be assessed after the adverse event collection.

- A blood sample for CCI [redacted] quantification must be taken immediately after EOI and at 2 hours after EOI. Vital signs must be assessed prior to blood sampling.
- See section 8.3 for procedures following IMP administration.

CCI [redacted]

9.9 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood collected from each patient will be approximately 360 mL during the study.

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

CCI [redacted]

9.10 Treatment Compliance

Responsible study personnel will administer the infusions of the 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[60]

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, safety COAs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

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

Serious adverse event – is any adverse event that:

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

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

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

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

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

Suspected unexpected serious adverse reaction – 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*[42]) and related to a medicinal product by either the investigator or Lundbeck.

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

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

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

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

Assessment of Causal Relationship

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

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

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

Assessment of Outcome

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

- *Recovered* – the patient has recovered completely, and no symptoms remain.
- *Recovering* – the patient's condition is improving, but symptoms still remain.

- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

10.1.3 Study-specific Adverse Event Definitions

10.1.3.1 Infusion-related Reactions

An *IRR* is any sign or symptom experienced by a patient during the infusion of the IMP or any event occurring on the day of the IMP infusion after the infusion was started.

Clinical manifestations of IRRs vary. Examples of IRRs include anaphylactoid reactions, anaphylaxis, dizziness, flushing, hypotension, nasal congestion, nausea, and syncope.

10.1.3.2 Management of Reactions to Study Drug

There are no specific antidotes to an infusion of Lu AG09222.

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. Any events believed to be allergic reactions should be discussed with the medical monitor.

CCI [redacted]

10.2 Pregnancy

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

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

If the partner of a man participating in the study becomes pregnant, the *outcome* of the pregnancy should be followed if the partner agrees. The partner must sign a pregnant partner informed consent form to allow the investigator to collect information to report to Lundbeck.

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

10.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events) must be recorded on an *Adverse Event Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded, if available. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

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

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

10.4 Reporting Serious Adverse Events

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

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

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

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

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

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

Lundbeck will assume responsibility for reporting sudden unexpected adverse reactions (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[61] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ECs.

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

10.5 Treatment and Follow-up of Adverse Events

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

The investigator must follow up on non-serious adverse events until resolution or the Safety Follow-up Visit/Contact, whichever comes first. At the Safety Follow-up Visit/Contact, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

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

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

The investigator must follow up on patients with a clinically significant out-of-range clinical safety laboratory test value at the Primary Outcome or Withdrawal Visit for up to 12 weeks. If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established

by the Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). If further follow-up visits are made, these must be documented in the patient's medical records and not in the eCRF.

10.6 Data Monitoring Committee

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

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 PPD. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

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

11.1.2.2 Serious Adverse Event Fallback Forms

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

11.1.3 External Data

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

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

- eDiary data
- COA data
- ECG data
- Clinical safety laboratory data (including blood sampling for serology [HBsAg, anti-HBc, anti-HBs, anti-HCV]) and blood sampling for other screening [e.g., β-hCG, FSH])
- IMP quantification data
- CCI [redacted] quantification data
- CCI [redacted] analysis data
- CCI [redacted] data
- ADA and NAb data
- CCI [redacted]

11.2 Database Release

The database will be declared to be complete and accurate by mutual agreement between the CRO and Lundbeck. Once the database release has been approved by both parties, the database will be released and unblinded in accordance with CRO procedures, as agreed by Lundbeck.

11.3 Retention of Study Documents at the Site

11.3.1 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.

11.3.2 Other Study Documents

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

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

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

12 Monitoring Procedures

Prior to allowing patients to participate in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site.

If the investigator does not have a patient's medical records, the investigator/designee must attempt to obtain copies or a written summary of relevant medical records from the doctor who had treated the patient earlier and include the pertinent documentation in the patient's medical records at the site. The investigator/designee must obtain migraine history, general medical history, recent medication taken, and previous migraine preventive medication treatment failures (see section 9.1.1 for definition) within the 10 years prior to the Screening Visit. The signed *Informed Consent Form* must be obtained prior to the Screening Visit if the investigator/designee needs to obtain relevant documentation from the patient's treating physician. The investigator can delegate the task of collecting this information to appropriate site staff, but it is still the investigator's responsibility to ensure that the patient fulfils the eligibility criteria (this includes checking that adequate documentation has been obtained) prior to screening the patient.

Acceptable documented evidence of previous migraine preventive medication failures is as follows:

- Medical record with medication's name, treatment stop and start dates, dose level and reasons for discontinuation, OR
- If the investigator is also the treating physician, the investigator can provide a dated and signed written note with the above information, OR
- If the investigator is not the treating physician and medical records are not available/sufficient, the investigator/designee can either:

- Interview the treating physician to confirm the above information and document the interview with date and name of treating physician in the medical records, OR
- Interview the patient to obtain the above information, then contact the treating physician to confirm the information and document the contact in the medical records with date and name of treating physician.

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

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

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

13 Audits and Inspections

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

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

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

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

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

14 Protocol Compliance

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

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

15 Study Termination

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

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

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

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

16 Statistical Methodology

16.1 Responsibilities

H. Lundbeck A/S will perform the statistical analyses described below. CCI [redacted]

16.2 Analysis Sets

The following analysis sets will be used for the analyses:

- All patients enrolled set (APES) – all enrolled patients
- All patients randomized set (APRS) – all randomized patients
- All patients treated set (APTS) – all patients in the APRS who received an infusion of IMP
- Full analysis set (FAS) – all patients in the APTS who have a valid baseline assessment of the number of MMDs and a valid assessment of the number of MMDs over Weeks 1 to 4
- Full analysis set long term (FAS-LT) – all patients in the APTS who have a valid baseline assessment of the number of MMDs and at least one valid post-baseline assessment of MMDs (Weeks 1 to 4 or Weeks 5 to 8 or Weeks 9 to 12)
- CCI [redacted]

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

Safety will be reported based on the APTS. Efficacy in the treatment period will be reported for the FAS. Maintenance of effect covering efficacy in the treatment period as well as the safety follow-up period will be reported for the FAS-LT.

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 prior to Week 4, as well as the number of patients in each analysis set described in section 16.2.

The number of patients who completed or withdrew from the study will also be summarized.

The number of patients who withdrew prior to Week 4 will be summarized by treatment group and primary reason for withdrawal as well as by treatment group and all reasons for withdrawal.

The number of patients who did not complete the study will be summarized by treatment group and the reason for withdrawal from the study.

16.5 Demographics and Baseline Characteristics

Demographics (sex, age, and race), baseline characteristics (height, weight, and BMI), baseline efficacy variables, and other disease characteristics (including, but not limited to, headache location, CCI score, CM or EM, number of failed preventive migraine medications) will be summarized by treatment group.

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.

16.7 Exposure

All patients in the APTS are expected to receive only one single infusion of the IMP. The number of patients who received the treatment, number of patients with infusion interruption, number of days in the study, and duration of infusion will be summarized by treatment group. Randomized patients whose infusion took more than 45 minutes and patients who had their infusion interrupted will be listed with treatment group, infusion start date/time and end date/time, IRRs, total volume infused, 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 one-sided tests performed at the 5% significance level and all confidence intervals (CIs) will be 90% CIs, unless otherwise specified.

16.8.2 Primary Analysis of the Primary Endpoint

The clinical question to be answered with the primary analysis is: does Lu AG09222 prevent migraine in the target patient population?

The estimand that will be used to answer the clinical question is: the effect of Lu AG09222 that would be seen regardless of whether treatment was administered per protocol and if no preventive migraine therapy was used and all patients were able to continue in the study.

The treatments that will be compared are the treatment of interest, Lu AG09222, and the reference treatment placebo.

The population that will be evaluated is the FAS including the target population as described in this document.

The variable on which the primary analysis is based is the primary variable, change from baseline in the number of MMDs over Weeks 1 to 4, which summarizes eDiary data across Weeks 1 to 4. If acute rescue medication is successfully used during a day, this day counts as a migraine day (see section 9.1.2). See section 9.1.3 for definition of a Migraine Day, Headache Day and Compliant Day during the Screening Period. The same definitions will be used for the treatment period.

The following intercurrent events (IEs) have been identified:

- Use of acute rescue medication
- Use of preventive migraine therapy
- Treatment not administered per protocol

These IEs will be taken into account as follows: use of acute rescue medication or preventive migraine therapy (different from investigational medication) is taken into account using a composite strategy. Incorrect administration of treatment is handled using a treatment policy strategy.

The population level summary for the primary analysis is: the least-squares mean difference in change from baseline in the number of MMDs (Weeks 1 to 4) between the high dose of CCI and placebo, based on an analysis of covariance (ANCOVA) with baseline MMDs as covariate and treatment (placebo, low dose, high dose), population (EM or CM), and an interaction between the stratification factors (region and CCI

If withdrawal from study occurred, data obtained after withdrawal will be included in the analysis, and, if IEs occur after withdrawal from study (use of acute rescue medication or preventive migraine therapy), the methods described for handling IEs will be applied.

Missing data for MD assessments, will be handled as follows: if 13 days or less have been recorded during a 28-day period, the assessment for that 28-day period will be set to missing. If 14 or more days have been recorded, prorating will be used.

Full details of the statistical methods for handling IEs and missing data, will be described in the Statistical Analysis Plan.

16.8.3 Sensitivity Analyses of the Primary Endpoint

The impact of the imputation of the primary endpoint will be assessed in a sensitivity analysis, applying different measures of imputation. For patients experiencing an IE, the imputation strategy will depend on the type of IE.

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 Testing Strategy

The type 1 error will only be controlled for the primary analysis comparing the primary endpoint (change from baseline in MMDs [Weeks 1 to 4]) for the high dose of Lu AG09222 to placebo at a one-sided 5% significance level. Other analyses will be considered exploratory, and statistical significance will be considered indicative rather than confirmative for the finding.

16.8.5 Analysis of the Secondary Endpoints

For the secondary endpoints based on response rates, the estimand strategy will be the same as for the primary analysis, except that the population level summary will be the odds ratio comparing Lu AG09222 to placebo from a logistic regression model with baseline MMDs as covariate, treatment as a fixed factor, and population (EM or CM) and CCI [redacted]

In general, endpoints based on a change from baseline to Weeks 1 to 4 or to Week 4 will be analysed following the approach for the primary endpoint. For endpoints related to MMD or monthly headache day, the IE "Use of acute rescue medication" will be addressed using a composite strategy. For other endpoints, a treatment policy approach will be used for this IE.

16.8.6 Analysis of the Exploratory Endpoints

CCI [redacted] will be analysed using similar methods as for response rates for secondary endpoints. If no data have been recorded on the day after dosing, a value will be imputed based on rules specified in the SAP.

CCI

[redacted]

[redacted]

16.8.7 Analysis of Subgroups

Details of subgroup analyses will be specified in the SAP.

16.9 Safety Analyses

16.9.1 Analysis of Adverse Events

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

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date 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 TEAEs to Study Periods

TEAEs may be allocated to study periods (these will be defined in the SAP).

16.9.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, vital signs, ECG parameter values, weight and development of ADA (including NAb) will be summarized by treatment group. Potentially clinically significant values will be flagged and summarized.

The C-SSRS scores will be presented using the C-SSRS categorization. The numbers and percentages of patients with lifetime, baseline, or post-baseline suicide-related events based on the C-SSRS scores will be summarized by treatment group.

The individual C-SSRS scores will be listed, and patients with at least one suicide-related event based on the C-SSRS scores will be flagged.

Missing C-SSRS scores will not be imputed.

16.10 Sample Size and Power

Simulations were used to determine a sample size that ensured at least 80% power at a one-sided 5% significance level for detecting an effect of 2.1 on the CCI dose when using an ANCOVA with baseline MMD as a covariate and treatment and population (EM or CM) as fixed factors. A population with 30% EM and 70% CM patients was assumed with standard deviations of 3.8 and 6.1, respectively, which resulted in a standard deviation of 5.6 for the full population. The resulting required sample size is 86 patients per arm for the CCI dose and placebo. No formal power calculation was performed for the CCI dose. A sample size of 43 per arm was considered sufficient to evaluate the relevant endpoints for this dose, which results in a randomization ratio of 2:1:2. Adjusting for an expected 5% dropout rate, a total sample size of 230 will be required.

The cap of 30% for the EM population results in a similar precision (standard error) for the treatment estimates for the EM and CM populations.

Simulations are based on 10000 runs.

16.11 Statistical Analysis Plan

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

17 Clinical Study Report and Publications

17.1 Data Ownership

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

17.2 Clinical Study Report

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

17.3 Summary of Clinical Study Results

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

17.4 Publications

The results of this study will be submitted for publication.

Lundbeck will submit results information:

- to ClinicalTrials.gov
- to EudraCT

The primary publication based on this study must be published before any secondary publications. Authors of the primary publication must fulfil the criteria defined by the ICMJE.[62]

18 Indemnity and Insurance

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

19 Finance

19.1 Site Agreements

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

19.2 Financial Disclosure

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

19.3 Equipment

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

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Appendix I
Clinical Study Protocol
Authentication and Authorization

Clinical Study Protocol
Authentication and Authorization

Study title:	Interventional, randomized, double-blind, parallel-group, placebo-controlled study of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments
Study No.:	19678A
Edition No.:	3.0 (includes all Clinical Study Protocol changes since previous Edition 2.0) (the version No. in the footer is the system version No.)
Date of edition:	11 July 2022

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

Authentication

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

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

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	• Allowed if prescribed for non-migraine indications, if dose and regimen have been stable for at least 12 weeks prior to Screening Visit and until the Safety Follow-up Visit.
Antidepressants	• Allowed if prescribed for non-migraine indications, if dose and regimen have been stable for at least 12 weeks prior to Screening Visit and until the Safety Follow-up Visit
Antihypertensives	• Allowed if prescribed for non-migraine indications, if dose and regimen have been stable for at least 12 weeks prior to Screening Visit and until the Safety Follow-up Visit
Anti-impotence agents	• Allowed if the dose has been stable for at least 12 weeks prior to the Screening Visit and is expected to be maintained until the Safety Follow-up Visit (Week 12).
Anti-inflammatory agents	Allowed: • NSAID: Allowed as acute treatment for migraine (see restrictions under *anti-migraine agents*). Allowed if prescribed for non-migraine indications (e.g., acetylsalicylic acid for cardiovascular disease prevention or for treatment of infections). • Steroids: Inhalation steroids are allowed if prescribed, e.g., for asthma, provided the dose and regimen have been stable for at least 12 weeks prior to the Screening Visit and expected to be maintained until the Safety Follow-up Visit (Week 12). Disallowed: • Steroids: Do not use topical steroids <1 week prior to the Screening Visit until the Safety Follow-up Visit (Week 12). For systemic steroids See restrictions under *immunosuppressants.*
Anti-migraine agents	Allowed with restrictions: • Acute treatment of migraine (prescription or over-the-counter medication recommended by a healthcare professional) is allowed provided the treatments used have been stable for at least 14 days prior to the Screening Visit and expected to be maintained until the Safety Follow-up Visit (Week 12). At the discretion of the Investigator, on a case-by-case basis, changes that might be clinically warranted may be made after the Baseline Visit. • Any medications in preventive migraine treatment classes that are prescribed for medical conditions other than migraine prevention are allowed if they have been stable in terms of dose and regimen for at

Drug Class	Details
	least 12 weeks prior to the Screening Visit and until the Safety Follow-up Visit. Disallowed: • Do not use preventive migraine treatments <1 week prior to the Screening Visit until the Safety Follow-up Visit (Week 12). • Do not use oral anti-CGRP treatment <4 weeks prior to the Screening Visit and until the Safety Follow-up Visit (Week 12). • Do not use CGRP-directed monoclonal antibodies <24 weeks prior to the Screening Visit until the Safety Follow-up Visit (Week 12). • 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 the Safety Follow-up Visit (Week 12). • Do not use monoamine oxidase inhibitors, ketamine, methysergide, methylergonovine, or nimesulide <12 weeks prior to the Screening Visit and until the Safety Follow-up Visit (Week 12). • Do not use preventive injectable therapy (e.g., trigger point injections, extracranial nerve blocks, or facet joint injections) <8 weeks prior to the Screening Visit and until the Safety Follow-up Visit (Week 12).
Hormones	• Hormonal therapy (e.g., contraceptives, hormone replacement therapy) is allowed provided the dose and regimen have been stable for at least 12 weeks prior to the Screening Visit and expected to be maintained until the Safety Follow-up Visit (Week 12).
Immunosuppressants	• Do not use immunosuppressants (e.g., systemic steroids, TNF alpha inhibitors, methotrexate) <12 weeks (or at least 5 times the half-life of the medication) prior to the Screening Visit and until the Safety Follow-up Visit (Week 12).
Nicotine/Tobacco	• Allowed provided stable use for at least 14 days prior to the Screening Visit and until the Safety Follow-up Visit (Week 12).
Cannabinoids	• Are allowed provided a stable dose and regimen have been maintained for at least 12 weeks prior to the Screening Visit and are expected to be maintained until the Safety Follow-up Visit.
Opioid analgesics	• Prescription opiates (including single-ingredient or combination medications containing opiates, opioids, tramadol, or tapentadol) are allowed provided a stable dose and regimen have been maintained for at least 12 weeks prior to the Screening Visit and are expected to be maintained until the Safety Follow-up Visit (Week 12). These agents are allowed provided use has not exceeded 4 days per month for at least 12 weeks prior to the Screening Visit. These agents may be prescribed when considered medically indicated by the investigator during the study (including the screening period) providing their use does not exceed 4 days per month.

Drug Class	Details
Other interventions and devices for the treatment of migraine	Allowed with restrictions: • Non-pharmacological interventions and therapies for the treatment of migraine (e.g., behavioural therapy, physical therapy and acupuncture) are allowed provided their use has been stable for at least 12 weeks prior to the Screening Visit and is expected to be maintained until the Safety Follow-up Visit (Week 12). Disallowed: • Do not use CNS- and migraine-related devices (neuromodulation, neurostimulation) <8 weeks prior to the Screening Visit and until the Safety Follow-up Visit (Week 12).
Sedatives/hypnotics	• Barbiturates (including Fiorinal®, Fioricet®, or any other combination containing butalbital) are allowed provided a stable dose and regimen have been maintained for at least 12 weeks prior to the Screening Visit and are expected to be maintained until the Safety Follow-up Visit (Week 12). These agents are allowed provided use has not exceeded 4 days per month for at least 12 weeks prior to the Screening Visit. These agents may be prescribed when considered medically indicated by the investigator during the study (including the screening period) providing its use does not exceed 4 days per month. • Benzodiazepines are allowed provided a stable dose and regimen have been maintained for at least 12 weeks prior to the Screening Visit and are expected to be maintained until the Safety Follow-up Visit (Week 12). These agents may be prescribed when considered medically indicated during the study (including the screening period) and a stable dose and regimen are expected to be maintained.
Vaccinations	• Vaccinations (including COVID-19 vaccines) are allowed provided the vaccinations have been completed for at least 14 days prior to the Screening Visit. Vaccinations during the study are allowed providing the vaccination is received at least 3 days after the IMP administration. The vaccinations, including brand names, if used during the study must be reported as concomitant medications.

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	