Statistical Analysis Plan

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

Lu AG09222

Trial No.:	19678A
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PPD	PPD
SAP date:	29 March 2023

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List of Panels and Tables

List of Abbreviations and Definitions of Terms

ADA	anti-drug antibody
ANCOVA	analysis of covariance
APRS	all-patients-randomized set
APTS	all-patients-treated set
CCI	[redacted]
CCI	[redacted]
BMI	body mass index
CCI	[redacted]
CGRP	calcitonin gene-related peptide
CI	confidence interval
CM	chronic migraine
COA	clinical outcome assessment
C-SSRS	columbia suicide severity rating scale
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
CCI	[redacted]
FAS	full-analysis set
FAS-LT	full analysis set long term
HD	Headache day(s)
CCI	[redacted]
HLGT	high level group term
HLT	high level term
CCI	[redacted]
ICE	intercurrent event
IMP	investigational medicinal product
CCI	[redacted]
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MD	migraine day(s)
MHDs	monthly headache days
ML	maximum likelihood
MMDs	monthly migraine days
MMRM	mixed model for repeated measurements
MOH	medication overuse headache

CCI	[redacted]
NAb	neutralizing antibody
PACAP	pituitary adenylate cyclase-activating polypeptide
PCS	potentially clinically significant
PD	Pharmacodynamic(s)
PK	pharmacokinetic(s)
CCI	[redacted]
CCI	[redacted]
QT	specific ECG interval describing ventricular depolarization/repolarization
QTc	heart rate-corrected QT interval
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	statistical software package from the SAS® Institute
SMQ	standardised MedDRA Query
SOC	system organ class
TEAE	treatment-emergent adverse event
VAS	visual analogue scale

1 Objectives

The trial objectives and endpoints are summarized in Panel 1.

Panel 1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective • To evaluate the efficacy of Lu AG09222 for the prevention of migraine in participants 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)	[redacted]
[redacted] • [redacted]	[redacted]


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Objectives	Endpoints
Safety Objective • To evaluate the safety and tolerability of Lu AG09222	**Safety Endpoints** - Adverse events - 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 ADAs including NAbs - C-SSRS score

2 Trial Design

This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled Phase IIa trial 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 trial is defined as participants diagnosed with migraine as outlined in the International Classification of Headache Disorders Third Edition (ICHD-3) guidelines, with documented evidence of migraine occurring on CCI 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. Participants with a concurrent diagnosis of medication overuse headache (MOH) are allowed in the trial.

The aim is that approximately 30% of the randomized participants will have episodic migraine (EM; participants with headache occurring on <15 days). This will be ensured through a cap on the number of randomized EM participants. CCI

A total of 230 participants, recruited from specialist settings, will be randomly allocated via a randomization system to one of three treatment groups: Lu AG09222 CCI Lu AG09222 CCI , or placebo, in a ratio of 2:1:2.

Randomization will be stratified by region (North America versus Europe) and CCI

The total trial duration from the Screening Visit to the Safety Follow-up Visit is approximately 16 weeks and includes a Screening Period (28 to 30 days) and Safety Follow-up period is 12 weeks (includes the 4 weeks Treatment Period).

Participants 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).

Participants 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 ADAs including NAbs, CCI

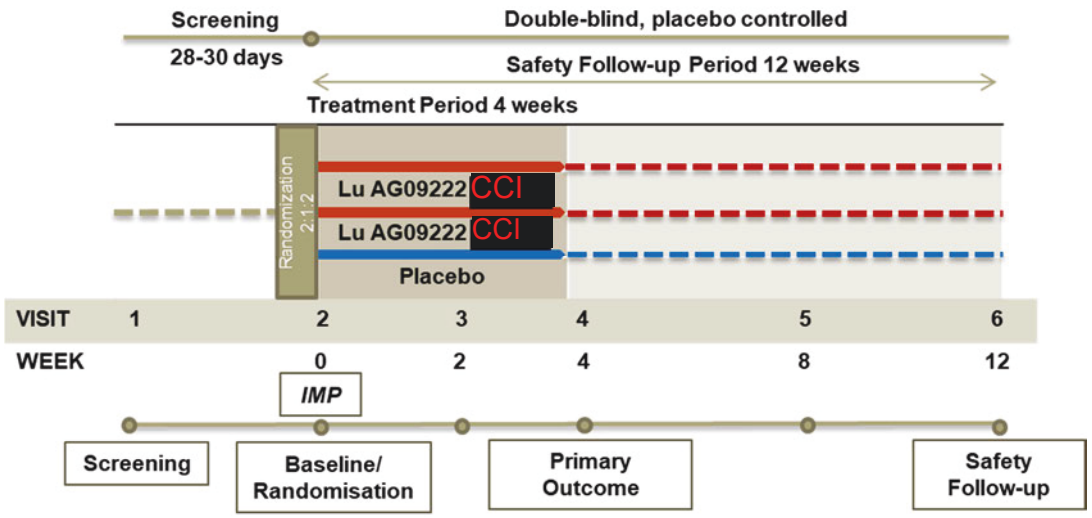
Participants must complete the eDiary recording of headaches that ended prior to infusion (i.e., for headaches not yet recorded in the eDiary).

Participants who complete the trial will attend a Safety Follow-up Visit at 8 weeks (Week 12) after the Primary Outcome Visit.

Participants 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.

The trial design is presented in Panel 2 (including the trial periods) and the scheduled trial procedures and assessments are summarized in Appendix II.

Panel 2 Trial Design



IMP = investigational medicinal product.

The trial consists of a screening period (28 to 30 days), a treatment period (4 weeks), and a safety follow-up period (12 weeks after IMP administration). IMP (Lu AG09222 CCI, Lu AG09222 CCI, or placebo) will be administered by intravenous infusion at the Baseline Visit. At Week 4, participants will complete the Primary Outcome Visit and will return to the clinic 8 weeks later (12 weeks after IMP administration) for a Safety Follow-up Visit.

3 COVID-19

For this trial, all participants are considered to have been enrolled after the beginning of the COVID-19 outbreak.

The following information is collected with regards to COVID-19:

- Whether a visit was done remotely due to COVID-19 including which assessments were/were not performed
- If a visit was not done, whether it was not done due to COVID-19
- Whether participants withdrew due to the COVID-19 situation
- Whether participants got diagnosed with COVID-19

The information collected with respect to COVID-19 will be presented in data listings.

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

4 Definitions

4.1 Definition of Baseline

For the endpoints based on daily recordings in the eDiary that are summarized in a monthly measure, the baseline value will be based upon the data recorded daily in the headache eDiary during the first 28 days following the Screening Visit.

For the endpoints based on daily recordings in the eDiary that are summarized in a weekly measure is derived as the average of the weekly values of the 28-day screening period.

For all other endpoints, the baseline assessment will be the latest available valid measurement taken prior to the administration of IMP.

4.2 Definition of Periods

The trial consists of the following periods:

- Screening Period (28-30 days): Starts at the Screening Visit (Visit 1) and continues up to start of Visit 2 IMP infusion (Week 0).
- Treatment Period (4 weeks): Starts at start of Visit 2 IMP (Week 0) infusion and continues up to and including Visit 4 (Week 4).
- Safety Follow-up Period (12 weeks): Starts at start of Visit 2 IMP (Week 0) infusion and continues up to and including the Safety Follow-up visit (Week 12).

4.3 Definition of Withdrawal

Participants who have received IMP infusion at Visit 2 and have withdrawn from the trial prior to the Primary Outcome Visit (Week 4), will be described as withdrawn from trial. The complementary group will be described as completed the trial.

4.4 Definition of Planned versus Actual Treatment

Participants will receive a single IV infusion of CCI Lu AG09222, or CCI Lu AG09222 or Placebo.

Planned treatment is defined as the treatment a participant was randomized to.

Actual treatment is defined as the treatment a participant actually received during the trial.

For reporting purposes, the following will be summarized by planned treatment:

- Efficacy
- Demographics and baseline characteristics
- Disposition
- eDiary compliance
- Concomitant medication

And the following will be summarized by actual treatment:

- Adverse events
- Exposure
- Immunogenicity
- Laboratory parameters, vital signs, ECG, and C-SSRS

Unless otherwise specified, data listings will display actual treatment.

4.5 Definition of Region

The following countries are included in the regions:

- North America: United States of America
- Europe: Czech Republic, Georgia, Denmark, Slovakia, Poland

4.6 Definitions for CCI Migraine Day, Headache Day, CCI

Participants will complete an eDiary, from the Screening Visit until the Safety Follow-up Visit or Efficacy Follow-up/Withdrawal Visit. In the headache diary, participants collect daily information on key symptoms and characteristics as mentioned in the definition of migraine (see section 4.6.2). For each day, the participant will record if they experienced any headaches. For each experienced headache, the start and stop date and time will be collected. The participant will record further daily information regarding headache characteristics (for instance, headache severity, additional symptoms) CCI Headache items will be assessed with a yes/no response; and severity will be rated as mild, moderate, or severe. Participants are expected to complete the eDiary on a daily basis during the trial regardless of whether they experienced a headache on that day.

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The eDiary-reported headache characteristics will be used in derivations of efficacy endpoints, including rules for handling missing data, as described in section 22.1.1.

For the purpose of endpoint derivations, CCI and migraine and headache days are defined as described below.

4.6.1 CCI

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4.6.2 Migraine Day

A migraine day is defined as a day with a headache that meets following criteria listed below:

1. A headache that:

Lasted 4 hours or more and had at least 2 of the following:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity

and had at least 1 of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

2. Or A headache that lasted 30 minutes or more and the participant had an aura with the headache (migraine with aura*)

3. Or A headache that lasted 30 minutes or more and meets 2 of the 3 following criteria (probable migraine**):

- Lasted 4 hours or more
- Had at least 2 of the following:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation by or causing avoidance of routine physical activity
- Had at least 1 of the following:
  1. Nausea and/ or vomiting
  2. Photophobia and phonophobia

4. Or a day with a headache that is successfully treated with a triptan, ergotamine, or other migraine-specific acute medication CCI [redacted]

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

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

<u>Further details on the definitions:</u>

CCI [redacted]

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4.6.3 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 (see section 4.6.2).

4.6.4 CCI

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4.6.5 CCI

CCI

4.6.6 CCI

CCI

5 Analysis Sets

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

- *all-participants-enrolled set* (APES) – all screened participants
- *all-participants-randomized set* (APRS) – all randomized participants
- *all-participants-treated set* (APTS) – all participants in the APRS who received an infusion of IMP
- *full-analysis set* (FAS) – all participants 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 participants 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)

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

The presentation and analyses of the primary endpoint, the secondary endpoint (50% MMD response) and safety tables (including exposure, concomitant medications and immunogenicity) will be based on APTS (see section 21.3).

CCI [redacted]

6 Descriptive Statistics

Unless otherwise specified, summary statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables, and counts and, if relevant, percentages will be presented for categorical variables.

Unless otherwise specified, data listings include site, treatment group, participant screening number, sex, age, race, baseline weight, BMI and CCI [redacted]

7 Participant Disposition

7.1 Summary of Participant Disposition

Participant disposition will be summarized by treatment group and include the number of participants in each analysis set defined in section 5, and the number of participants in the APTS who completed or withdrew from trial.

If any visits are changed from clinic to remote, a table will be provided presenting by type of visit (on clinic or remote) and treatment group.

7.2 Withdrawals

The number of participants who withdraw from the trial will be summarized by treatment group. The primary reason for withdrawal will be presented, as well as all reasons for withdrawal.

Participants who withdrew from the trial will be listed and the listing will include the number of days in the trial until withdrawal from the trial, the number of days on IMP, the primary reason for withdrawal, all reasons for withdrawal, and a flag if the drug code was broken.

Kaplan-Meier failure plots of time to withdrawal will be presented by treatment group. The time will be calculated from the date of IMP to the date of withdrawal in the Treatment Period. Participants who complete the Treatment Period will be regarded as censored at the End of Week 4 visit (Visit 4).

All tables, graphs, and listings will be based on the APTS.

8 Demographics and Baseline Characteristics

Demographics (sex, age, age group, race and region); baseline characteristics (height, weight, and BMI); baseline disease characteristics; and baseline efficacy variables will be summarized by treatment group.

All the demographics and baseline characteristics data described below will be summarized based on the APTS.

The baseline disease characteristics comprise of:

- age and age group (≤ 21 years, > 21 years) at first diagnosis of migraine
- time since first migraine ICHD-3 diagnosis (years)
- time since first migraine diagnosis group (≤ 15 years, > 15 years)
- current type of migraine (CM or EM)
- time since current migraine ICHD-3 diagnosis (years)
- CCI [redacted]

- CCI
- has an MOH diagnosis (yes/no)
- for women: whether migraines started before or after menarche
- for men: whether migraines started before or after puberty
- whether the start of migraine was related to any event

The eDiary reported baseline headache and migraine characteristics (data collected on daily basis during the screening period) that will be summarized are:

- number of baseline MMDs
- number of baseline MHDs
- CCI
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Concurrent as well as relevant past medical, neurological, and psychiatric disorders will be coded using the MedDRA, Version 25.0 (or later) and summarized by treatment group.

A concurrent medical, neurological, or psychiatric disorder is a disorder that is ongoing at the Screening Visit. A past medical, neurological, or psychiatric disorder is a disorder that ended prior to the Screening Visit. Social history will be summarized by treatment group.

Summaries of prior preventive treatment failure medications within 10 years prior to the Screening Visit will be presented by treatment group. The number and percentage of participants with each type of prior treatment failure (lack of efficacy, safety/tolerability, or contraindication) will also be presented by treatment group, as well as the number of prior preventive treatment failures.

9 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the *WHO Drug Dictionary* (WHO-DDE, version March 2022 or later).

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code, generic drug name and treatment group. Handling of missing or incomplete dates is specified in section 22.3.4.

The following categories will be used:

- Prior medications: Medications with a stop date before IMP infusion
- Concomitant medication: continued after IMP infusion or started at or after IMP infusion

The tables for prior and concomitant medications will be based on the APTS.

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All disallowed medications entered in the eCRF, which will be identified via a clinical review of the coded medication data in the eCRF, will be listed based on the APRS. The listing will include the generic drug name, the duration, the start and end dates, and dosing information.

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10 Exposure

For the IMP Visit, information related to infusion completed as planned in full (yes/no), infusion temporarily interrupted (yes/no), and infusion lasted longer than 30 (+15) minutes (yes/no), as well as descriptive statistics for the duration of infusion (this duration includes duration of any infusion interruptions), and duration of temporary interruptions will be summarized by actual treatment group.

The summaries will be based on the APTS. All infusion data will be listed.

11 CCI

12 Efficacy

12.1 General Efficacy Analysis Methodology

For the primary and the secondary endpoint concerning MMDs, the efficacy analyses will be based on the APTS. The analyses of the remaining efficacy endpoints with a single post-baseline timepoint will be based on the FAS, while the efficacy endpoints with multiple post-baseline timepoints will be based on the FAS-LT.

All the tables and graphs will be presented by treatment group.

For primary and secondary endpoints, statistical tests for comparisons of the CCI and CCI dose of Lu AG09222 versus placebo, will be reported with one-sided p-values and two-sided 90% confidence intervals.

In addition to the above, for primary, secondary, and all exploratory efficacy endpoints, two-sided 95% confidence intervals and p-values for the comparisons of the CCI and CCI dose of Lu AG09222 *versus* placebo will be reported.

All two-sided p-values are considered descriptive p-values.

The derivation of the endpoints is described in section 22.1.

12.2 Testing Strategy

The type 1 error will only be controlled for the primary analysis comparing the primary endpoint (the change from baseline in MMDs [Weeks 1 to 4]) for the CCI Lu AG09222 dose versus 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.

12.3 Analysis Methodology for the Primary Endpoint

12.3.1 Primary Estimand

The primary estimand 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.

The following intercurrent events (ICEs) will be addressed:

- Use of acute migraine-specific medication
- Use of preventive migraine therapy
- Use of non-migraine specific medication
- IMP not administered per protocol
- COVID-19 Vaccination during the Treatment Period – Treatment Policy Strategy

The attributes of the primary estimand are:

- The **treatment** condition of interest is the comparison of CCI Lu AG09222 to placebo without use of preventive migraine medication.
- The **population** of interest are participants with a diagnosis of migraine, with migraine occurring on CCI per month and headache occurring on ≤26 days.
- The **endpoint** to be considered is the change from baseline in MMDs (Weeks 1-4)
- The **population level summary** will be mean difference in the primary endpoint, comparing the effect of CCI Lu AG09222 to placebo.

Intercurrent events:

- use of acute migraine-specific medication implicitly a composite strategy is applied since the definition of the MMDs based on the ICHD-3 guideline includes the impact of the use of acute migraine-specific medication on whether a day is considered a migraine day
- use of acute non-migraine specific medication, that is reported to have successfully treated the headache will be addressed using a treatment policy strategy.
- use of preventive migraine therapy will be addressed using a hypothetical strategy, where data collected after preventive medication intake is considered missing and are handled using missing data analysis methods (see section 22.1.3)
- infusion interruptions or termination before full dose is received will be addressed using a treatment policy strategy.

12.3.2 Strategies for Addressing Intercurrent Events in Primary Estimand

Use of Acute Migraine-Specific Medication – Composite Strategy

A composite strategy will be applied to address the use of acute medication: if acute migraine-specific medication (CCI [redacted]) is used during a day, and is reported to have successfully treated the headache, this day counts as a migraine day. See section 4.6.2 for the definitions of a Migraine Day during the Screening Period. The same definitions will be used for the Treatment Period. The eDiary data collected are used regardless of these intercurrent events.

For presentation of this intercurrent event, see section 9.

Use of Preventive Migraine Treatment – Hypothetical Strategy

A hypothetical strategy will be applied to address the use of preventive migraine treatment by setting the eDiary data collected after the use of preventive medication as missing and applying multiple imputation where, for the missing observations, information is borrowed from non-missing observations from the same treatment group.

For presentation of this intercurrent event, see section 9.

Use of Non-migraine Specific Medication – Treatment Policy Strategy

A treatment policy strategy is used to address the intercurrent event of use non-migraine specific medication, that is reported to have successfully treated the headache in which the eDiary data collected are used regardless of these intercurrent events.

IMP not Administered per Protocol – Treatment Policy Strategy

Infusions not completed as planned, infusions temporarily interrupted, and infusions that lasted longer than 30 (+15) minutes could impact the efficacy. These intercurrent events will be addressed using a treatment policy strategy, in which the eDiary data collected are used regardless of these intercurrent events.

For presentation of these intercurrent events, see section 10.

COVID-19 Vaccination During the Treatment Period – Treatment Policy Strategy

A treatment policy strategy is used to address the intercurrent event of getting COVID-19 vaccination during the Treatment Period, in which the eDiary data collected are used regardless of these intercurrent events.

12.3.3 Primary Analysis of the Primary Endpoint

The main estimator for the primary estimand is defined as the least squares mean difference for the mean change from baseline in the number of MMDs over Weeks 1 to 4 between

CCI Lu AG09222 *versus* the placebo group, obtained from an ANCOVA with baseline MMDs as a covariate and treatment (placebo, CCI Lu AG09222, CCI Lu AG09222), population (EM, CM), and CCI

Missing data for the MMD over Weeks 1 to 4 (CCI) will be addressed by using Multiple Imputation performed in which the remaining missing data will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the corresponding randomized treatment group.[1]

200 simulations will be performed to generate the datasets that will be analysed using the specified ANCOVA model above. These analyses will be combined using Rubin's rule to form a unique point estimate and standard error, taking into account the uncertainty of the imputation.[2] The combined least square means difference between CCI Lu AG09222 and the placebo group will be evaluated at a one-sided 5% significance level and constitutes the primary analysis.

The SAS® code for this analysis is shown in Appendix IV.

The analysis will be performed for the first month of the trial, derived as specified in section 22.1.1. The term "month" refers to 4-week periods.

This analysis will include all participants in the APTS.

12.3.4 Rationale for Selected Analysis Method for the Primary Endpoint

The MMDs are considered continuous data, and they are analysed using methods based on observations following a normal distribution. An ANCOVA analysis has been chosen for the primary analysis. Covariates are included in the model based on an approach that includes key factors to represent trial design, namely treatment group, CCI baseline MMD and migraine population (EM, CM) to adjust for baseline differences in disease characteristics.

12.3.5 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be conducted on the APTS:

- CCI
- Assessing the impact of missing data using placebo-based multiple imputation (pMI): An analysis will be performed using pattern-mixture model (PMM), in which the CCI missing data CCI will be imputed using a regression-based multiple imputation method, based

on the imputation models established from the placebo group. 200 simulations will be performed to generate the datasets that will be analysed using the model described in section 12.3.3.These analyses will be combined using Rubin's rule to form a unique point estimate and standard error, taking into account the uncertainty of the imputation. The SAS® code for this sensitivity analysis is shown in Appendix IV.

12.3.6 CCI

12.4 Analysis Methodology for the Secondary Endpoints

The following endpoints will be analysed:

- 50% MMD response: ≥50% reduction from baseline in MMDs (Weeks 1 to 4)
- change from baseline in the number of MHDs (Weeks 1 to 4)

For 50% MMD response, the estimand strategy will be the same as for the primary analysis (see section 12.3.1), except that the population level summary will be the odds ratio comparing Lu AG09222 CCI and Lu AG09222 CCI to placebo from a logistic regression model with baseline MMDs as covariate and treatment, population (EM, CM), CCI as fixed factor.

The logistic regression model will be fitted using the ML method and the logit link function. In case of convergence issues, the Firth's bias-reducing penalized likelihood method will be applied.

The 200 simulated datasets from the primary analyses (section 12.3.3) will be dichotomized into responders (≥50% reduction of MMDs) and non-responders. Each of the dichotomized datasets will be analysed using the logistic regression model specified above. For each analysis the results will then be transformed into a test statistic, which is approximately standard normally distributed under the null hypothesis of no treatment effect, following the approach by Ratitch et al,.[3] The transformed statistics will be combined across the 200 data sets, using PROC MIANALYZE to generate a combined set of estimates, test statistics and p-value for these tests. The SAS® code for this analysis is shown in Appendix IV.

The combined odds ratios for Lu AG09222 CCI and CCI compared to placebo will be presented with one-sided p-values and 90% CIs. In addition, the differences in the combined response rates for Lu AG09222 CCI and CCI *versus* placebo will be presented.

The analysis will be based on the APTS.

For the secondary endpoint, change from baseline in the number of MHDs (Weeks 1 to 4), the estimand strategy will be the same as for the primary analysis (see section 12.3.1).

The endpoint will be analysed with an ANCOVA with baseline MHDs as a covariate and treatment (placebo, CCI Lu AG09222, CCI Lu AG09222), population (EM, CM), CCI as fixed factor.

The analysis will be based on the FAS.

12.5 CCI

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- CCI

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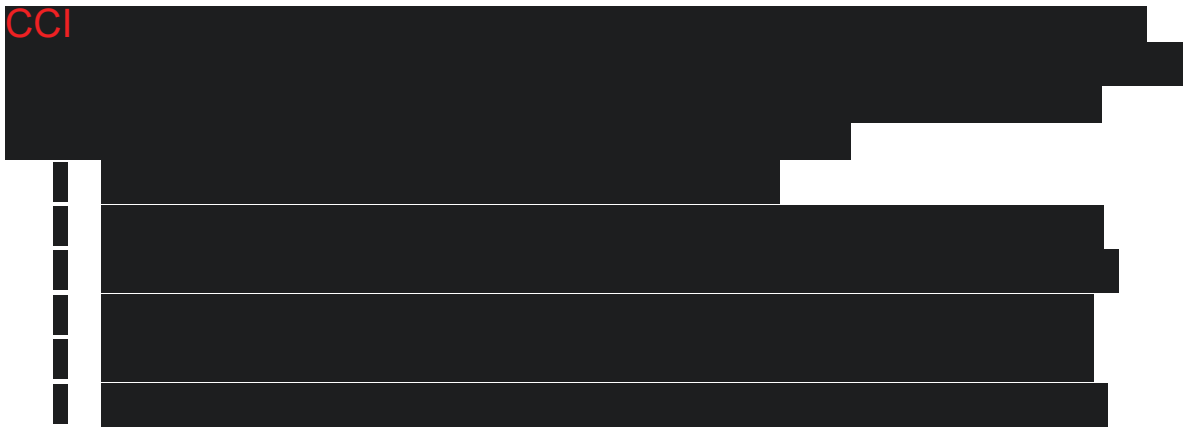
- CCI [redacted]

CCI [redacted]



13 Safety

13.1 Adverse Events

13.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

All the tables and graphs will be presented by treatment group.

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order based on the percentages of participants with these adverse events in the Lu AG09222 CCI group.

Unless otherwise specified, the summaries of adverse events will include the number and percentage of participants with an adverse event and number of events. In tables displaying SOC or preferred terms, participants are counted only once within each SOC or preferred term.

Listings of adverse events will be sorted by site, treatment group, participant screening number, preferred term, verbatim, adverse event start date, adverse event stop date, the date of IMP infusion, the time since IMP infusion, duration of the adverse event, date of death, action taken, causality, intensity, seriousness, and outcome.

For adverse events that change in intensity, each intensity will be included. In listings of adverse events, start or stop dates will be displayed as collected also in case of partially or completely missing dates.

13.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 25.0 or later.

13.1.3 Classification 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 participant signed the *Informed Consent Form* and prior to the date and time of the dose of IMP.
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts during or after administration of the dose of IMP, or a pre-treatment adverse event that increases in intensity or becomes serious during or after administration of the dose of IMP.

For handling of adverse events with incomplete start dates to facilitate this classification, see section 22.3.5. Note that adverse events with incomplete start dates will be classified as treatment-emergent simply if the imputed start date is on or after the date of IMP infusion, since the start time of the adverse event will not be imputed, unless the investigator in such a case has assessed that the causality to IMP is *not related - prior to IMP*.

An adverse event is considered causally related to the use of the IMP when the causality assessment by the investigator is *probable* or *possible*. If the causality assessment is missing, the adverse event is considered possibly causally related.

13.1.4 Presentation of Adverse Events

All adverse events will be listed for the APRS, including a flag for TEAEs.

An overview of the numbers and percentages of participants with TEAEs, serious adverse events (SAEs), TEAEs leading to infusion interruption, TEAEs leading to withdrawal, and of participants who died will be provided based on the APTS. For TEAEs, SAEs, and TEAEs leading to withdrawal, the total number of events will be included.

All pre-treatment adverse events will be summarized and listed for the APRS, separately.

13.1.5 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided for the APTS:

- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs by sex and preferred term
- TEAEs with an incidence ≥2% and 5% in any treatment group by preferred term
- causally related TEAEs by SOC and preferred term
- TEAEs by severity (*mild*/*moderate*/*severe*), SOC, and preferred term
- causally related TEAEs by severity, SOC, and preferred term
- TEAEs occurring on the day of dosing after infusion start by SOC and preferred term

For TEAEs occurring on the day of dosing after infusion start, TEAEs with missing start times will also be included.

13.1.6 Presentation of Deaths

All the adverse events in participants who died will be listed for the APRS.

13.1.7 Presentation of Serious Adverse Events

All the SAEs will be listed for the APRS.

Treatment-emergent SAEs for the APTS will be summarized by:

- SOC and preferred term
- preferred term

13.1.8 Presentation of Adverse Events Leading to Withdrawal

All the adverse events leading to withdrawal will be listed for the APRS.

TEAEs leading to withdrawal will be summarized by:

- SOC and preferred term
- preferred term

13.1.9 Presentation of Adverse Events Leading to IMP Infusion Interruption

All the adverse events leading to IMP infusion interruption will be listed for the APRS.

TEAEs leading to IMP infusion interruption will be summarized based on APTS by:

- SOC and preferred term
- preferred term

13.1.10 CCI

[redacted]

13.2 General Methodology for Other Safety Data

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

All the tables will be presented by treatment group.

The denominators for the summaries of a given variable will be based on the number of participants with non-missing values at a given visit or during the assessment period.

Descriptive statistics for the safety variables, both absolute values and changes from baseline, will be presented by visit.

The number and percentage of participants with at least one PCS value at any post-baseline assessment time point will be summarized by variable. All available assessments will be included in the evaluation of PCS values.

The number and percentage of participants with values out-of-reference range and/or PCS range will be summarized by variable, visit, and last post-baseline assessment.

For participants with post-baseline PCS values, listings will be provided including all the values for those participants for the variable, with flagging of PCS values and out-of-reference-range values.

All the adverse events occurring in participants with post-baseline PCS values will be listed by treatment group and participant screening number; the listing will include the PCS value, the assessment date, the change from baseline in PCS value, the preferred term for the adverse event, and the start date and stop date of the adverse event. The PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

13.3 Clinical Safety Laboratory Test Data

13.3.1 Data Presentation

The PCS criteria for the clinical safety laboratory tests are in Table 2.

The clinical safety laboratory test values will be presented in Système International (SI) units.

Fasting lipid and fasting glucose concentrations will be presented in separate tables from the overall laboratory tables.

For urine dipsticks, for which the results are categorical values (for example, negative, trace, 1+, 2+), the number and percentage of participants will be summarized by visit for each test. The microscopy results will be listed by assessment time point for participants with findings.

13.3.2 Anti-drug Antibody Including Neutralizing Antibody Assessments

Analysis of specific anti-Lu AG09222 antibodies is restricted to participants in the APTS who are treated with Lu AG09222.

For participants with pre-existing antibodies at Baseline, the number and percentage of participants who are positive for anti-Lu AG09222 antibody will be summarized. In addition, the number and percentage of participants who develop anti-drug antibodies to Lu AG09222 during the trial will be summarized at each scheduled visit. Denominators for percentages will be the total number of samples taken for the specified visit. For participants with ADA, neutralizing properties of anti-Lu AG09222 antibodies will also be summarized.

Participants with a positive anti-Lu AG09222 antibody result will be listed.

All the adverse events occurring in participants with positive anti- Lu AG09222 antibody or with pre-existing antibodies at Baseline, will be listed. The listing will include the ADA result, the assessment date, the preferred term for the adverse event, and start date and stop date of the adverse event. The ADA results and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

In addition, summaries of TEAEs by SOC and preferred term, summaries for TEAEs included in the SMQ Hypersensitivity Narrow by SOC and preferred term will be provided for participants who are ADA-positive and ADA-negative separately.

Furthermore, the potential impact of ADA on efficacy will be explored by providing summaries of change from baseline in monthly migraine days for participants who are ADA-positive and ADA-negative separately.

13.3.3 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[4] using the following criteria:

- ALT or AST >2×, >3×, >5×, >10×, or >20×ULN
- total bilirubin (BILI) >2×ULN
- alkaline phosphatase (ALP) >1.5×ULN
- ALT or AST >3×ULN AND total bilirubin >1.5× or >2×ULN

Participants fulfilling any of the criteria will be listed, and the listing will include all the ALT, AST, BILI, and ALP values for those participants, sorted by assessment date and time in ascending order. If a criterion for a test is fulfilled, the value will be flagged with the highest criterion fulfilled (for example, AST >3×ULN, >5×ULN, >10×ULN, or >20×ULN).

In addition, assessment time points for participants for whom Hy's Law is potentially fulfilled will also be flagged in the listings (pHYL):

- ALT or AST >3×ULN AND
- alkaline phosphatase <2×ULN AND
- total bilirubin ≥2×ULN

The number of participants who met any of the criteria specified above at any post-baseline visit will be summarized. In the summaries, each participant will be counted only once using the maximum assessment, or the most severe for the combined criteria. The summaries will

also include the number of potential Hy's Law cases. If any participants fulfil Hy's Law (all 3 criteria fulfilled), information collected related to this finding will be presented in data listings.

13.4 Vital Signs and Weight

The PCS criteria used for vital signs and weight are the Lundbeck standard PCS criteria shown in Table 3.

13.5 ECGs

The PCS criteria used for the ECG parameters are the Lundbeck standard PCS criteria described in Table 4.

In addition to the tables and listings specified in section 13.2, the absolute values and changes from Baseline in QTcF will also be summarized categorically by visit and treatment. The categories that will be used are as follows for the absolute QTcF values:

- QTcF interval < 450 msec
- QTcF interval 450 - 480 msec
- QTcF interval > 480 - 500 msec
- QTcF interval > 500 msec

The categories that will be used for the change from baseline QTcF values are:

- QTcF interval increase from baseline > 30 msec
- QTcF interval increase from baseline > 60 msec

Furthermore, the number and percentage of participants being classified as having either a *normal*, *abnormal but not clinically significant*, or *abnormal and clinically significant* ECG result based on the overall interpretation of the ECG from the investigator will be summarized by visit and treatment group.

13.6 Other Safety Endpoints

13.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Scores

The C-SSRS was administered:

- for lifetime (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening that collects a lifetime recall
- for the past 12 months at screening (using the *Baseline*/*Screening Version*) – the C-SSRS assessment at screening that focuses on the last 12 months
- at baseline (using the *Since Last Visit Version*) – the C-SSRS assessment at baseline that collects information since the previous visit

- post-baseline (using the *Since Last Visit Version*) – the C-SSRS assessments after baseline

The numbers and percentages of participants with lifetime, past 12 months, baseline, or post-baseline suicide-related events based on the C-SSRS will be summarized by treatment group. For each summary, the most severe item with an answer "Yes" for each participant according to the ordering given in Panel 6 is displayed. For the post-baseline assessments, the summaries will be by treatment group and period and the most severe item with an answer "Yes" for the whole period for each participant related to suicidal ideation and/or behaviour will be summarized.

The number and percentage of participants with *no suicidal ideation or behaviour* will be included in the summaries.

Panel 6 C-SSRS Scores

C-SSRS Score		Related to:
1	Wish to be dead	Suicidal ideation
2	Non-specific active suicidal thoughts	
3	Active suicidal ideation with any methods (not plan) without intent to act	
4	Active suicidal ideation with some intent to act, without specific plan	
5	Active suicidal ideation with specific plan and intent	
6	Preparatory acts or behaviour	Suicidal behaviour
7	Aborted attempt	
8	Interrupted attempt	
9	Non-fatal suicide attempt	
10	Completed suicide (only applicable for the post-baseline assessments)	

The C-SSRS scores will be summarized by visit based on the APTS for participants with at least one post-baseline C-SSRS assessment, regardless of whether they had a baseline C-SSRS assessment.

Missing C-SSRS scores will not be imputed.

Positive responses to *non-suicidal self-injurious behaviour* will be summarized separately.

For participants with any post-baseline suicidal behaviour (C-SSRS scores of 6 to 10), listings will be provided including all C-SSRS scores for those participants; C-SSRS scores related to suicidal behaviour will be flagged.

14 CCI

CCI

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15 Pharmacokinetic/Pharmacodynamic Analyses

CCI

16 CCI

CCI

17 Blinded Data Reviews

The quality of the trial will be overseen by performing blinded data reviews during the conduct of the trial. The reviews may include, but are not limited to, data quality, protocol adherence, and the appropriateness of design assumptions, including the sample size assumptions.

An independent Safety Data Monitoring Committee (DMC) will regularly monitor the participants' safety data according to the *DMC Charter*. The DMC will have access to unblinded information for the double-blind treatment for each participant. Members of the DMC will not be involved in other trial-related tasks.

18 Interim Analyses

No interim analyses are planned.

19 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 and allowing for stopping for futility. A population with 30% EM and 70% CM participants 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 participants 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% withdrawal 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.

20 Statistical Software

The statistical software used will be SAS®, Version 9.4 or later.

21 CCI

21.1 CCI

21.2 CCI

CCI

21.3 CCI

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21.4 CCI

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21.5 CCI

CCI

CCI

21.6 CCI

CCI

- CCI [redacted]

[redacted]

[redacted]

22 Details on Data Handling

22.1 Derived Variables

22.1.1 eDiary

22.1.1.1 Determination of Migraine Days and Headache Days

Headache day:

- A day is considered a headache day if a headache (as identified through a unique headache ID) has been reported to take place on that day with a duration of at least 30 minutes on that day, or if the day is a migraine day.
- A day is considered a non-headache day if one or more headaches (as identified through a unique headache ID) have been reported to take place on that day, but none

of them make the day qualify as a headache day as defined above. Or no headaches have been reported to take place on that day, but the headache diary was completed on that day, confirming that the participant did not have a headache to report.

- A day is considered a missing observation for headache day, if it is not a headache day or a non-headache day, as defined above.

Migraine day:

- A day is considered a migraine day if a headache (as identified through a unique headache ID) has been reported to take place on that day and fulfils the criteria for a migraine on that day (based on the criteria specified in section 4.6.2).
- A day is considered a non-migraine day if one or more headaches (as identified through a unique headache ID) have been reported to take place on that day and headache characteristics have been reported for all headaches on that day, but none of them make the day qualify as a migraine day as defined above. Or no headaches have been reported to take place on that day, but the headache diary was completed on that day, confirming that the participant did not have a headache to report.
- A day is considered a missing observation for migraine day, if information (e.g. headache characteristics) is missing in the headache diary to be able to classify the day as a migraine day or a non-migraine day.

If characteristics/symptoms for the same headache (identical headache ID) are reported more than once within the same day, then that day is considered a migraine day, if at least one set of characteristics make the day qualify as such.

22.1.1.2 Monthly Migraine Days, CCI [redacted]

The following describes the derivation of MMDs.

CCI [redacted]

For a given headache, determine whether it is a migraine attack as defined in section 4.6.4. If that is the case, then each day of the headache with a headache duration of at least 30 minutes or where the day itself fulfils the Migraine Day definition in section 4.6.2 is considered a migraine day according to Derivation method 1.

CCI [redacted]

4-Week Intervals

4-week intervals are considered for the following endpoints:

- change from Baseline in the number of MMDs (Weeks 1 to 4)
- change from Baseline in the number of MMDs (Weeks 5 to 8)
- change from Baseline in the number of MMDs (Weeks 9 to 12)

For Baseline and each 4-week period post-baseline, the MMDs/MHDs will be derived as the number of migraine days within each 28-day interval using the imputation rules described below. The following 4-week periods post-baseline are considered: Weeks 1 to 4, Weeks 5 to 8 and Weeks 9 to 12.

CCI

22.1.1.3 Migraine/CCI Response Variables

The following describes the derivation for response for monthly migraine/CCI days.

The following response variables will be derived: 50%, CCI A responder is defined as a participant who achieves a ≥50%, CCI reduction in MMDsCCI respectively, compared to the baseline MMDsCCI The derivation of these response endpoints will be based on the MMD CCI

For each 4-week interval after IMP dosing, the response status of a participant will be derived based on the percentage change from baseline in MMDsCCI. If the MMDs CCI value is missing for the 4-week interval in question, the response status will also be missing.

22.1.1.4 CCI

22.1.1.5 CCI

22.1.1.6 CCI

- CCI

[redacted]

[redacted]

[redacted]

[redacted]

22.1.1.7 CCI

[redacted]

[redacted]

[redacted]

22.1.1.8 CCI

[redacted]

- CCI [redacted]

[redacted]

22.1.2 CCI [redacted]

22.1.2.1 CCI [redacted]

[redacted]

22.1.2.2 CCI [redacted]

[redacted]

22.1.2.3 CCI [redacted]

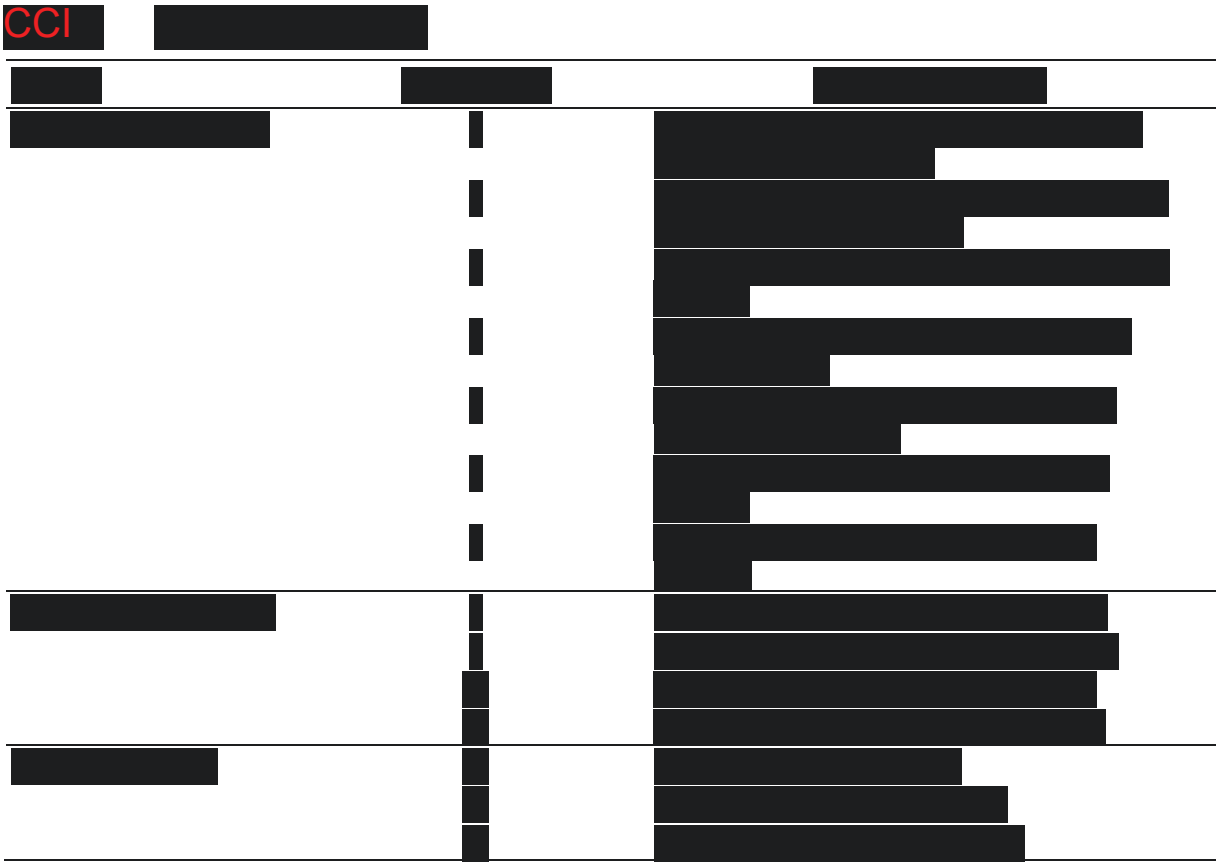
[redacted]

CCI [redacted]

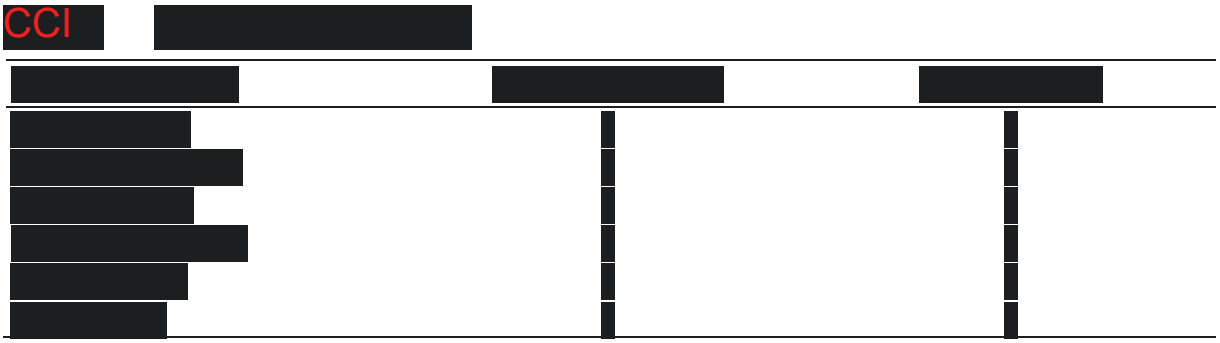
22.1.2.4 CCI [redacted]

CCI [redacted]

CCI



CCI



CCI

CCI

22.1.2.9 CCI

22.1.3 Handling of Data After ICE "Use of Preventive Therapy"

In the case of the intercurrent event "use of preventive therapy" occurs (see section 12.3.2), the data collected after preventive medication intake will be disregarded and set to missing.

22.2 Assigning Data to Visits

See section 4.1 for definition of Baseline values.

22.2.1 Safety Variables

Laboratory Tests, Vital Signs, Body Weight, ECG and C-SSRS

Assessments at unscheduled visits and withdrawal visits will be assigned to a nominal visit, according to the visit windowing specified in Panel 6. Assessments for participants not receiving an infusion of IMP will be assigned to Visit 2 (Baseline).

Panel 6 Visit Windows - Laboratory Tests, Vital Signs, Body Weight, ECG and C-SSRS

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Screening Visit)	-4	-28	Day -28 and before IMP infusion
V2 (Baseline Visit)	0	0	Same day as IMP infusion (Day 0) and prior to IMP infusion on that date
V3	2	14	After start of IMP infusion to Day 21
V4	4	28	Day 22 to Day 41 after start of IMP infusion

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V5	8	56	Day 42 to Day 69 after start of IMP infusion
V6	12	84	Day 70 to Day 98 after start of IMP infusion

If there is more than one assessment at a visit (either due to multiple assessments or because an unscheduled or withdrawal visit assessment is mapped to a nominal visit with an already existing value) the value that will be used in summary tables by visit will be the one closest to the nominal day for the visit but prioritizing values from scheduled visits above values from withdrawal or unscheduled visits. In the ordering of multiple values, assessments without recorded time will come after assessments with recorded time and the first in the ordering will be selected.

22.3 Handling Missing or Incomplete Dates/Times

22.3.1 Missing Headache End Date and Time

If the end date and time for a headache recorded in the eDiary is missing, the headache end date and time will be imputed with the end of trial date.

Note that for each participant, it is only possible to have a missing end date and time for the last headache entered, since a participant needs to complete a headache entry in order to report a new headache in the headache eDiary.

22.3.2 Withdrawal Date

Missing withdrawal dates will not be imputed and time to withdrawal from treatment will not be calculated for missing withdrawal dates.

22.3.3 Medical Disorder Start and Stop Dates

Incomplete dates will not be imputed. Classification of events into *concurrent medical disorders* or *past disorders* will be based on the reported ongoing status.

22.3.4 Medication Start and Stop Dates

Imputation of incomplete or partially missing dates will be performed in order to document the assigned categories specified in section 9.

The algorithm for imputing the start dates will follow the one used for imputing adverse event start dates, see section 22.3.5.

For imputing stop dates, the following will apply, where UK and UKN indicate unknown or missing day and month, respectively:

- UK-MMM-YYYY: Medication end date is imputed with the last day of the month
- UK-UKN-YYYY: Medication end date is imputed with 31-DEC-YYYY

Medications marked as ongoing are considered concomitant medications.

22.3.5 Adverse Event Start and Stop Dates

Imputation of partially or completely missing dates will be included in the data to document the treatment-emergent status of the adverse event and assignment of the adverse event to a reporting period. For an adverse event with an imputed start date, the classification of the event as treatment-emergent will depend only on whether the imputed date is the same as the date of infusion and not the timepoint of the infusion, since start times for adverse events will not be imputed. No duration will be calculated for adverse events with incomplete start-or-stop dates or for ongoing adverse events.

Imputation will follow the algorithm below. If an imputed start date after this procedure is after the end date, the start date will be set to the end date.

Start Dates

Participants With No IMP Infusion

For participants who have not been treated, the imputation of the adverse event start date will be performed as follows, where UK and UKN indicate unknown or missing day and month, respectively:

- UK-MMM-YYYY: The start date will be imputed with either the first day of the month or the date of Visit 1. The date of Visit 1 will be used if that is the later of the two and if it is within the specified month and year
- UK-UKN-YYYY: The start date will be imputed with either JAN 1 or the date of Visit 1. The date of Visit 1 will be used if it is within the specified year.

If the adverse event start date is completely missing, it will be set equal to the date of Visit 1.

Participants Who Received an IMP Infusion

For participants who have been treated, the imputation of adverse event start dates will be performed as follows:

UK-MMM-YYYY:

- If the year and month are equal to the year and month of treatment start date, the adverse event start date is imputed with the date of the dosing of IMP

- If the year is equal to the year of treatment start date: If the month is prior to the treatment start date, the adverse event start date is imputed with the last day of the month. If the month is equal to the month of the treatment start date, see above. If the month is after the month of the treatment start date, the adverse event start date is imputed with the first day of the month
- If the year is prior to treatment start date, the adverse event start date is imputed with the last day of the month
- If the year is after the year of treatment start date, the adverse event start date is imputed with the first day of the month

UK-UKN-YYYY:

- If the year is equal to the year of treatment start date, the adverse event start date is imputed with treatment start date
- If the year is prior to the year of treatment start date, the adverse event start date is imputed with 31-DEC-YYYY
- If the year is after the year of treatment start date, the adverse event start date is imputed with 01-JAN-YYYY

If the adverse event start date is completely missing, it will be set equal to treatment start date.

End Dates

Missing adverse event end dates will not be imputed.

22.4 Data With Multiple Records

22.4.1 Dose Changes in Medication

Dose changes in medications are recorded on multiple rows in the dataset, with different start and stop dates. When classifying medications into categories (see section 9), each dose is considered a separate medication, and the same medication can be assigned to several categories for the same participant. Within a category, multiple entries contribute as a single count.

22.4.2 Changes in Intensity or Seriousness of Adverse Events

Changes in adverse event intensity or seriousness are recorded on multiple rows in the dataset. An adverse event that changes in intensity or seriousness in a period will contribute to the count of events as a single event.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used. The maximum intensity is searched for in events with changes, as well as over repeated events based on the preferred term. Adverse events for which information on intensity is missing will be classified as *severe*.

Adverse events for which information on seriousness is missing will be classified as serious.

References

1. Little R and Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics. 1996; 52: 1324-1333.
2. Rubin, DB. Multiple imputation for nonresponse in surveys. New York: Wiley; 1997.
3. Ratitch B, Lipkovich I, O'Kelly M. Combining analysis results from multiply imputed categorical Data. PharmaSUG. 2013; Paper SP03.
4. United States Food and Drug Administration (US FDA). Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009.

Appendix I

Statistical Analysis Plan

Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Trial title:	Interventional, randomised, double-blind, parallel-group, placebo-controlled trial of Lu AG09222 for the prevention of migraine in patients with unsuccessful prior preventive treatments
Trial No.:	19678A
SAP date:	29 March 2023

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

Authentication

PPD

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Authorization

PPD

PPD

Appendix II

Trial Procedures and Assessments

Trial Procedures and Assessments

Table 1 Trial 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								

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**
Randomization		√						
Efficacy Assessments								
eDiary daily recording[f,g]	√	√[j]	√	√	√	√[c,k]	√ [k]	√ [k]
CCI								
CCI								
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]		√		√	√	

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**	**Telephone**
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**
Examinations (neurological)[q]	√	√[m]				√		
C-SSRS[r]	√	√[m]	√	√	√	√	√	
CCI								
CCI		√[m]		√				
CCI		√[m]		√				
CCI		√[m]						
CCI		√[m]		√		√	√	
Other Trial 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]	√							
CCI								
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 β-hCG = beta-human chorionic gonadotropin; CCI BL = baseline; CCI C-SSRS = Columbia-Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; 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; PACAP = pituitary adenylate cyclase-activating peptide; CCI PO = primary outcome; CCI ; RNA = ribonucleic acid; 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 CCI (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 trial (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.
f. At the Screening Visit, the patient must be assisted with the provisioning and training of the eDiary CCI 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. CCI
j. CCI 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. CCI
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 , CCI ADA including NAb, CCI), urine sampling (for

clinical safety laboratory and pregnancy tests), CCI , 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 CCI . 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-trial 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 trial in consultation with the sponsor.

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

r. The CCI C-SSRS will be administered by the authorized rater. For this trial, 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

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 trial 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/trial 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 trial. 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*.

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Appendix III

ICHD-3 Guidelines for Migraine

ICHD-3 Guidelines for Migraine

1.1 Migraine without 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.

1.2 Migraine with Aura

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.

Appendix IV

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CCI [redacted]

[redacted]

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[redacted]

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Appendix V

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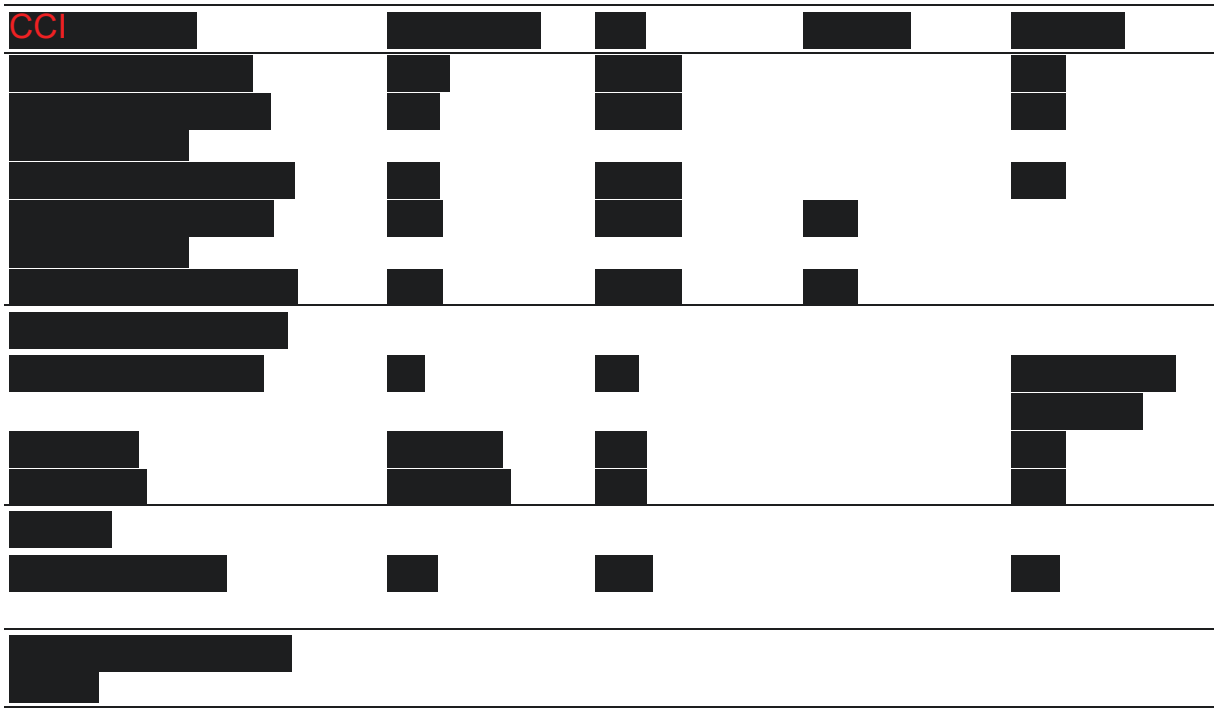

Table 3 PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Variable	CDISC Term	Unit	PCS Low	PCS High
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperature	TEMP	ºC	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value.

Table 4 PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS Low	PCS High
Absolute Time Interval				
PR interval	PRAG	Msec		≥ 260
QRS interval	QRSAG	Msec		≥ 150
QT interval	QTAG	Msec		≥ 500
Derived Time Interval				
Heart rate	EGHRMN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCBAG	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCFAG	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value.

Appendix VI

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CCI [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	