J1H-MC-LAJB(a) Statistical Analysis Plan Version 1

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3451838 in Adults With Treatment-Resistant Migraine

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Statistical Analysis Plan: J1H-MC-LAJB(a): A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of LY3451838 in Adults with Treatment-Resistant Migraine

LY3451838

Phase 2 study of LY3451838 in in Adults with Treatment-Resistant Migraine. Patients will be randomly assigned to 2 treatment arms: LY3451838 or placebo.

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Protocol J1H-MC-LAJB(a)
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly on date provided below.

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1. Table of Contents

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
CAS	Cranial Autonomic Symptoms
CRF	Case report forms
ITT	Intent-to-treat
MH	Medical history
min	Minimum
max	Maximum
MedDRA	Medical dictionary for regulatory activities
NCI CTCAE	Common Terminology Criteria for Adverse Events published by the National Cancer Institute
NE	Not evaluable
PACAP38	Pituitary adenylate cyclase activating polypeptide-38
PK	Pharmacokinetics
SAE	Serious adverse event
SOC	System organ class
STD	Standard deviation
WHO	World health organization

2. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a patient receives study drug or any other protocol intervention.

3. Study Objectives

Table 3.1 provides the objectives and endpoints of the study.

Table 3.1. Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
To test the hypothesis that a single IV dose of LY3451838 is superior to placebo in the prevention of migraine in treatment-resistant migraine patients	The mean change from baseline in the number of monthly migraine headache days during the 1-month treatment phase (episodic and chronic migraine) [a]
Secondary Objectives	
To compare LY3451838 with placebo with respect to prevention of monthly headache days	The mean change from baseline in the number of monthly headache days during the 1-month treatment phase
To compare LY3451838 with placebo with respect to 50% response rate	The percentage of patients with ≥50% reduction from baseline in monthly migraine headache days during the 1-month treatment phase
To evaluate the safety and tolerability of a single dose of LY3451838 in treatment-resistant migraine patients	TEAEs SAEs
To characterize the pharmacokinetics of LY3451838 following a single IV dose in treatment-resistant migraine patients	LY3451838 Cmax and AUC
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[redacted]

[a] Episodic migraine is defined as 4 to 14 migraine headache days and <15 headache days per 1-month period in the prospective baseline period. Chronic migraine is defined as at least 15 headache days per 1-month period in the prospective baseline period, of which at least 8 are migraine.

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4. Study Design

4.1. Summary of Study Design

Study LAJB is a multicenter, randomized, double-blind, parallel, placebo-controlled study of LY3451838 in patients who meet the International Classification of Headache Disorders version 3 (ICHD-3) criteria for a diagnosis of migraine with or without aura, or chronic migraine, and who have previously failed 2 to 4 categories of standard-of-care treatments for migraine prevention. The study has 4 periods, including the screening period, baseline for J1H-MC-LAJB(a) Clinical Protocol Page 9 LY3451838 eligibility, double-blind treatment phase, and follow-up assessment of headache episodes and related information.

4.2. Determination of Sample Size

The study will screen an estimated 110 potential patients to ensure randomization of approximately 60 migraine patients. Enrollment will be stratified by type of migraine, episodic versus chronic, and patients will be randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum. CCI [redacted]

The analysis will be conducted using all randomized patients, and it is assumed that approximately 2% of the patient population will dropout during the 28 days treatment period.

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Enrolling approximately 60 patients who are stratified by type of migraine, episodic versus chronic, and randomly assigned to either LY3451838 or placebo in a 1:1 allocation ratio within each stratum will provide approximately CCI [redacted]

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4.3. Method of Assignment to Treatment

Following a 1-month prospective baseline period, eligible patients will be stratified by type of migraine (episodic or chronic) and then randomly assigned in a 1:1 ratio within each stratum to receive LY3451838 or placebo. Treatment assignment will be determined by a computer-generated randomization sequence using an interactive web response system (IWRS).

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5. A Priori Statistical Methods

5.1. General Considerations

Efficacy analyses will be conducted on the full analysis set (FAS). Safety analyses will be conducted on the safety analysis set (SAF) which are described in Section 5.2. When mean change from baseline is assessed, the patient will be included in the analysis only if the patient has a baseline and a postbaseline measurement.

In general, for analyses of numeric outcome measures during the treatment phase, baseline value is defined as the last observation at or before Visit 3. Treatment effects will be evaluated based on a 2-sided significance level of 0.05.

A Bayesian analysis will be performed for the primary efficacy endpoint, and the corresponding frequentist analyses will be conducted as a supplemental analysis. All other statistical inference will be performed using frequentist methods.

For continuous variables, descriptive statistics will include the number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using the number and percentage of patients.

SAS® software version 9.4 or higher will be used to perform statistical analyses, unless otherwise specified.

The following terms and data handling conventions defined in Table 5.1 will be used in the analysis.

Table 5.1. Date and Timing Conventions

Term	Definitions or Rule

Study Day	If assessment is on or after date of first treatment dose then
	(date of assessment) – (date of first study treatment dose) + 1
	If assessment precedes first treatment dose then
	(date of assessment) – (date of first study treatment dose)

Baseline value	Baseline value is defined as the last reported assessment on or before the first dose (or discontinuation, if no treatment is given).
Screening period	Date of informed consent (Visit 1) through the day prior to Visit 2; includes all dates of study participation for those without Visit 2.
Baseline period	Visit 2 date through the day prior to study drug administration (for those receiving study drug); Visit 2 date through end of study participation for those who participating in Visit 2 but not receiving study drug.
Study treatment period	The 1-month double-blind treatment phase begins on the date of study drug administration (Visit 3) and continues through date of Month 1 visit (Visit 5) for those participating in Visit 5; continues through study withdrawal for those withdrawing prior to Visit 6 (Month 1.5). If patients do not attend Visit 5 but continue on study, the end of study treatment period will be the expected date of Visit 5 (i.e.30 days after Visit 3).

Follow-up period	Patients who continue on study after Visit 5 (or beyond expected date of Visit 5, if patient does not attend Visit 5 but attends later visits) will enter the follow-up period the day after the Visit 5 date (or expected date, where relevant), and continue for up to 140 days post-dose.

5.2. Analysis Sets

The following analysis sets used for analysis are defined in Table 5.2 below.

Table 5.2. List of Analysis Sets

Analysis Set	Definitions or Rule
Enrolled Patients	Includes all patients who have signed the informed consent
Screen Failures	Includes all patients who have signed the informed consent but are not treated or randomized
Full Analysis Set (FAS)	The FAS will include all patients who have been randomized to study treatment following the intent to treat (ITT) principle. Patients in this set will be grouped according to their allocated treatment. All patient characteristic and efficacy data will be presented using the FAS.
Per-protocol Set (PPS)	The PPS will include all patients who have been randomized to study treatment and did not have any major protocol deviations. Patients in this set will be grouped according to their allocated treatment. Additional efficacy analyses may be conducted on PPS.
Safety Analysis Set (SAF)	The SAF will include all patients who have been randomized to study treatment and have received at least 1 dose of study treatment (LY3451838 or placebo). Patients will be grouped according to actual treatment received.

5.3. Handling of Dropouts or Missing Data

Missing data imputation for adverse event medical history, and concomitant medication dates will be performed as follows. Imputed dates will be used to determine treatment-emergent or concomitant status, but imputed portions of dates (or times) will not be displayed in listings.

Start dates/Dates of onset:

- Completely missing: impute as patient's treatment date
- Year present, month and day missing:
  - If year is the same as year of treatment date, impute as treatment date
  - Otherwise, impute as December 31st
- Month and year present, day missing:
  - If month and year are the same as treatment date, impute as treatment date
  - Otherwise, impute as last day of the month
- Time missing:
  - If same date as treatment date, impute as start time of treatment
  - Otherwise impute as 23:59

End dates / resolution dates:

- Completely missing: impute as date of study completion or withdrawal from study
- Year present, month and day missing: Impute as December 31st
- Month and year present, day missing: Impute as the last day of the month
- Time missing: Impute as 23:59

5.4. Multiple Comparisons/Multiplicity for Endpoints

No adjustment for multiplicity is planned for this study.

5.5. Patient Disposition

A summary and listing of patient disposition using the FAS will be provided at the end of the study. All patients who discontinue from the study will be identified in the listing. If known, a reason for their discontinuation will be given in the listing.

5.6. Protocol Deviation

Important protocol deviations are defined as deviations from the protocol that potentially could have a meaningful impact on study conduct or on the primary efficacy, safety, or pharmacokinetics (PK) outcomes for an individual participant. The criteria for identifying study important protocol deviations will be defined within the appropriate protocol-specific document and will be reviewed as part of the ongoing data cleaning process and data evaluation.

All important protocol deviations will be identified and documented prior to unblinding to confirm exclusion from the PPS. A summary and a listing of all important protocol deviation will be produced using the FAS.

5.7. Demographics and Baseline Characteristics

The following will be summarized by treatment group using the FAS.

- Demographics (age, sex, ethnic origin, race)
- Baseline characteristics (height, weight, body mass index)
- Migraine and/or headache-related measures from the ePRO diary per 1-month baseline period
  - Number of monthly migraine headache days
- Number of prior migraine preventive treatment failures from the list in protocol Section 6.1 (Inclusion Criterion #6):
- Medical history and pre-existing conditions

Medical history and preexisting conditions will be summarized by descending frequency of preferred term (PT) within system organ class (SOC). Medical history is defined as illness(es) that ended prior to the signing of informed consent. Preexisting conditions are defined as either ongoing (concomitant) or has ended (prior) on or after the date of informed consent.

5.8. Treatment Compliance

The study drug will be administered at the site during Visit 3. Drug administration information will be listed. All patients will receive CCI of either the treatment or placebo. Patients will be classified as receiving the complete drug administration if they receive all CCI

5.9. Electronic Patient Reported Outcomes Diary Compliance

Electronic patient reported outcomes diary compliance at each 1-month period (including baseline and 1-month treatment phase) will be calculated. Diary compliance at each period is calculated as:

Actual number of diary days in the period / Expected number of diary days in the period * 100

Diary compliance is defined using an 80% threshold.

A summary of diary compliance will be produced by treatment arm using the FAS.

5.10. Concomitant Therapy

The proportion of patients who received concomitant medication and acute medications will be summarized and listed using the FAS. Concomitant medication refers to medication used to prevent migraines. The list of concomitant medication is found in section 7.8 of the protocol table 7.1.

5.11. Efficacy Analyses

5.11.1. Primary Endpoint and Primary Methodology

The primary analysis will be performed using a linear model for the change from baseline in the monthly number of migraine headache days within the Bayesian framework. The model will include randomized treatment and type of migraine as fixed effects and the baseline number of monthly migraine headache days as a covariate. The analysis will use a non-informative prior for the treatment effect. CCI

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Additionally, if the compliance rate for a monthly interval is ≤50%, then the number of migraine headache days derived from the ePRO diary data for that 1-month period will be considered missing.

5.11.2. Sensitivity Analyses for Primary Endpoint

All patients have over 50% diary entry compliance in the 1-month treatment phase and no subject has monthly migraine headache days set to missing. Therefore, the sensitivity analysis will not be performed.

5.11.3. Supplemental Analysis on the Primary Endpoint

A second supplemental analysis for the primary endpoint will include a change in baseline for monthly migraine headache day using post-baseline data to month 3. The 3-month migraine headache days will be normalized to 30 days as done with the 1-month treatment phase data.

5.11.4. Secondary and Exploratory Efficacy Endpoints

Due to insufficient enrollment only the primary endpoint is to be evaluated. The data for all secondary and exploratory endpoints is available in the SDTMs for any analyses to be performed if needed.

5.12. Safety Analyses

5.12.1. Adverse Events

TEAEs are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with baseline phase. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, the event is considered as treatment-emergent for the specific postbaseline period.

For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

For events that are sex-specific, the denominator and computation of the percentage will include only patients from the specific sex.

The safety and tolerability of treatment will be assessed by summarizing (using standard descriptive statistics) and listed on the SAF. The following parameters will be reported:

- TEAEs
- SAEs
- AEs leading to discontinuation
- Potential hypersensitivity events
- AEs related to injection site reactions
- Vital signs
- Physical and neurological examinations
- ECGs
- Laboratory measurements
- CBB

Additional analysis will be performed as required.

5.13. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic and PK/pharmacodynamic analyses are the responsibility of the PK scientist. Details will be provided in the PK/pharmacodynamic analysis plan.

5.14. Evaluation of Immunogenicity

The data for the evaluation of immunogenicity is available in the SDTMs for any analyses to be performed if needed.

5.15. Other Analyses

5.15.1. Health Outcome Analyses

The data for health outcome analyses is available in the SDTMs for any analyses to be performed if needed.

5.15.2. Migraine Specific Quality of Life (MSQ)

The data for MSQ is available in the SDTMs for any analyses to be performed if needed.

5.15.3. Headache Impact Test (HIT-6)

The data for HIT-6 is available in the SDTMs for any analyses to be performed if needed.

5.15.4. Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS) Data

The data for C-SSRS is available in the SDTMs for any analyses to be performed if needed.

5.15.5. Cognition

The data for cognition is available in the SDTMs for any analyses to be performed if needed.

5.16. Interim Analyses and Data Monitoring

An interim analysis is planned when data from all randomized patients have completed the 1-month treatment period. The interim efficacy results may be used for internal decision-making to trigger planning activities associated with the investigational product.

No adjustment of Type I error will be performed as the study will not be stopped for efficacy, and no modification of Study LAJB is expected based on these interim results.

The assessment would be conducted by a sponsor assessment committee with a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or to the blinded study team until the study has been unblinded.

5.17. Planned Exploratory Analyses

None.

5.18. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA Preferred Term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/patients in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

5.19. Annual Report Analyses

The Annual Report is replaced by the Development Safety Update Report (DSUR). The following reports will be produced for the DSUR:

- Exposure
- Disposition
- Demographics
- Listing of patients who died during the DSUR period
- Discontinuations due to adverse event during the DSUR Period.

For further details on these reports, see the DSUR collaboration site: http://lillynetcollaboration.global.lilly.com/sites/GMRS_GPS/Surv/dsur/default.aspx?PageView=Shared

6. References

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