Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled Study with an Open-Label Period on Efficacy and Safety of Fremanezumab in Chinese Adults with Migraine

Study Number TV48125-CNS-30088

NCT05458011

SAP Approval Date: 25 January 2024

STATISTICAL ANALYSIS PLAN

Study TV48125-CNS-30088 with Protocol Amendment 02

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients

Phase 3

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: TV48125-CNS-30088

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients

Statistical Analysis Plan for:

- ☒ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Amendment: NA

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CM	chronic migraine
CNS	central nervous system
CRF	case report form
CS	compound symmetry
CSR	clinical study report
ECG	electrocardiography/electrocardiogram
EM	episodic migraine
EOS	end of study
EOT	end of treatment (visit)
ET	early termination
FSH	follicle-stimulating hormone
GGT	gamma glutamyl transpeptidase
HDL	high-density lipoprotein
HGB	hemoglobin
ICE	intercurrent event
ICHD-3	International Classification of Headache Disorders, 3rd revision
IHS	International Headache Society
IMP	investigational medicinal product
INN	international nonproprietary name
INR	international normalized ratio
IRT	interactive response technology
ITT	intent-to-treat
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LS	least square

Abbreviation	Term
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed-effects repeated measures
MNAR	missing not at random
NSAID	non-steroidal anti-inflammatory drug
PD	protocol deviations
PGIC	Patient Global Impression of Change
PP	per-protocol
PT	preferred term
Q2	quarter 2
Q3	quarter 3
R&D	Research and Development
SAP	statistical analysis plan
SAS®	Statistical Analysis System
sc	subcutaneous(ly)
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Study TV48125-CNS-30088, (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study with an Open-Label Treatment Period of Fremanezumab Administered Subcutaneously Monthly or Quarterly for the Preventive Treatment of Migraine in Adult Chinese Patients), and was written in accordance with GSD-SOP-702 (Statistical Analysis Plan).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (eg, other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. Primary and Secondary Study Objectives and Endpoints

Note that, for endpoints that are based on a monthly average, "baseline" refers to the monthly average value during the 28-day baseline period.

The primary and secondary study objectives and endpoints are the following:

Objectives	Endpoints
The **primary objective** of the study is to demonstrate the efficacy of fremanezumab administered as monthly and quarterly subcutaneous (sc) injections to adult Chinese patients with migraine. The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.	The primary endpoint is the mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of investigational medicinal product (IMP).
The **secondary objective** of the study is to further demonstrate the efficacy of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine. The secondary efficacy analyses will consider all fremanezumab-treated patients as 1 group.	The secondary endpoints are as follows: • mean change from baseline in the number of migraine days during the 4-week period after the 1st dose of IMP • mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP • proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP • mean change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered as monthly and quarterly sc injections to adult Chinese patients with migraine.	The safety/tolerability endpoints are as follows: • occurrence of adverse events throughout the study • clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at specified time points

Objectives	Endpoints
	• vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit (Note: Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.) • 12-lead electrocardiogram (ECG) findings at specified time points • use of concomitant medication for adverse events during the study • number (%) of patients who did not complete the study due to adverse events • clinically significant changes in physical examinations • assessment of the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to sc fremanezumab • assessment of the ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

ADA=antidrug antibody; ECG=electrocardiogram; IMP=investigational medicinal product; sc=subcutaneous.

1.2. Pharmacokinetic and Other Objectives and Endpoints

Pharmacokinetic and other endpoints for the double-blind treatment period to address the objective to further characterize fremanezumab safety, efficacy, and pharmacokinetics are as follows:

- assessment of plasma concentration of fremanezumab during the 12-week period after the 1st dose of investigational medicinal product (IMP) and at the follow-up visit using a population pharmacokinetic modeling approach

[redacted]

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a multicenter, randomized, double-blind, placebo-controlled study with an open-label treatment period to evaluate the efficacy, safety, and tolerability of monthly and quarterly sc fremanezumab for the preventive treatment of migraine in adults. The study will consist of a screening visit, a baseline period (4 weeks), a 12-week double-blind treatment period, a 12-week open-label treatment period, and a follow-up period lasting approximately 3 months after the last dose of IMP (ie, 2 months after the end of treatment [EOT]/early termination [ET] visit). A follow-up visit 3 months after the last dose of fremanezumab will occur for ADA blood sample collection.

The total duration of patient participation in the study is planned to be approximately 9 months.

This study will include female and male patients, aged 18 to 70 years, inclusive, with a history of migraine (as defined by the International Classification of Headache Disorders, 3rd revision [ICHD-3] criteria [IHS 2018, CMAPS 2016]) for at least 12 months prior to screening and a prospectively documented diagnosis of migraine confirmed via a review of headache data recorded daily in an electronic headache diary device during a 28-day baseline period.

Up to 30% of patients will be allowed to continue on a stable dose of 1 preventive migraine medication listed in the study protocol for migraine prevention or for other chronic conditions that they were using before screening (patients must have been taking a stable dose of these medications for at least 2 months of consecutive use prior to screening and do not expect to change dosing regimens or to change to another medication during the treatment phase of the study). Patients will be allowed to use acute medications to treat breakthrough migraines as needed, with the exception of medications containing opioids and barbiturates, which cannot be used on more than 4 days during the screening period for the treatment of migraine or for any other reason. Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dose/regimen for at least 2 months (consecutive) before screening.

After completing the informed consent process (screening visit [visit 1]), patients will be screened for eligibility. Eligible patients will enter a 28-day baseline period. Headache information will be captured daily during the screening/baseline period and treatment period using an electronic headache diary device.

After completing the baseline period, patients will be asked to return to the study center on day 1 (visit 2). Patients who have confirmed migraine and meet all other eligibility criteria (including electronic headache diary device compliance criteria during the 28-day baseline period) will be randomly assigned in a 1:1:2 ratio to 1 of 3 treatment groups:

- fremanezumab 225 mg sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; one 225 mg injection and 2 placebo injections at visit 2 and one 225 mg injection at visits 3 and 4
- fremanezumab 675 mg sc once a quarter (once at the beginning of the 12-week double-blind treatment period), for a total of 1 dose; three 225 mg injections at visit 2 and 1 placebo injection at visits 3 and 4 or

- placebo sc once a month (approximately every 4 weeks [28 days]), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4

Patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration.

During the 12-week open-label treatment period, patients will receive fremanezumab 225 mg sc once a month (approximately every 4 weeks) for a total of 3 doses (one 225 mg injection at visits 5, 6, and 7).

At the end of the open-label treatment period (4 weeks after the last dose), an EOT study visit (visit 8) will be scheduled. Patients should return to the care of their treating physicians after visit 8. Patients should be treated with standard of care after withdrawal from or termination of the 24-week treatment period/study, as appropriate.

(Note: For this study, monthly dosing refers to dosing approximately every 4 weeks [28 days].)

Randomization using electronic interactive response technology (IRT) will be stratified based on migraine type (chronic migraine (CM) vs episodic migraine (EM)) and baseline preventive medication use (from protocol appendix K) to ensure balance. Blinded treatment will be administered sc once monthly (ie, approximately every 4 weeks), for a total of 3 doses. First treatment administration will occur at visit 2 (day 1), and additional doses will be administered at visits 3 and 4.

The Patient Global Impression of Change (PGIC) scale, safety evaluations, and blood draws for pharmacokinetic and immunogenicity analysis will be performed throughout the study according to the schedule of study procedures and assessments (see study protocol).

Patients will have treatment evaluations performed at visit 8 (EOT visit), approximately 4 weeks after administration of the final dose of study drug.

Follow-up visits for ADA sample collection will occur approximately 1 month and 3 months after the last dose of study drug (visit 7), at the EOT/ET visit (visit 8) and at the end of study visit (visit 9), respectively.

Patients who discontinue treatment prematurely should be encouraged to continue to attend the regular scheduled visits and complete the prescribed safety and efficacy evaluations through the EOT/ET visit and the follow-up visit, if at all possible.

Patients who both discontinue treatment and also withdraw from the study should have EOT/ET visit procedures/assessments (see study protocol) performed on the last day that the patient receives the IMP or as soon as possible thereafter. The patient should also return for the follow-up visit approximately 3 months after the last dose of IMP if at all possible.

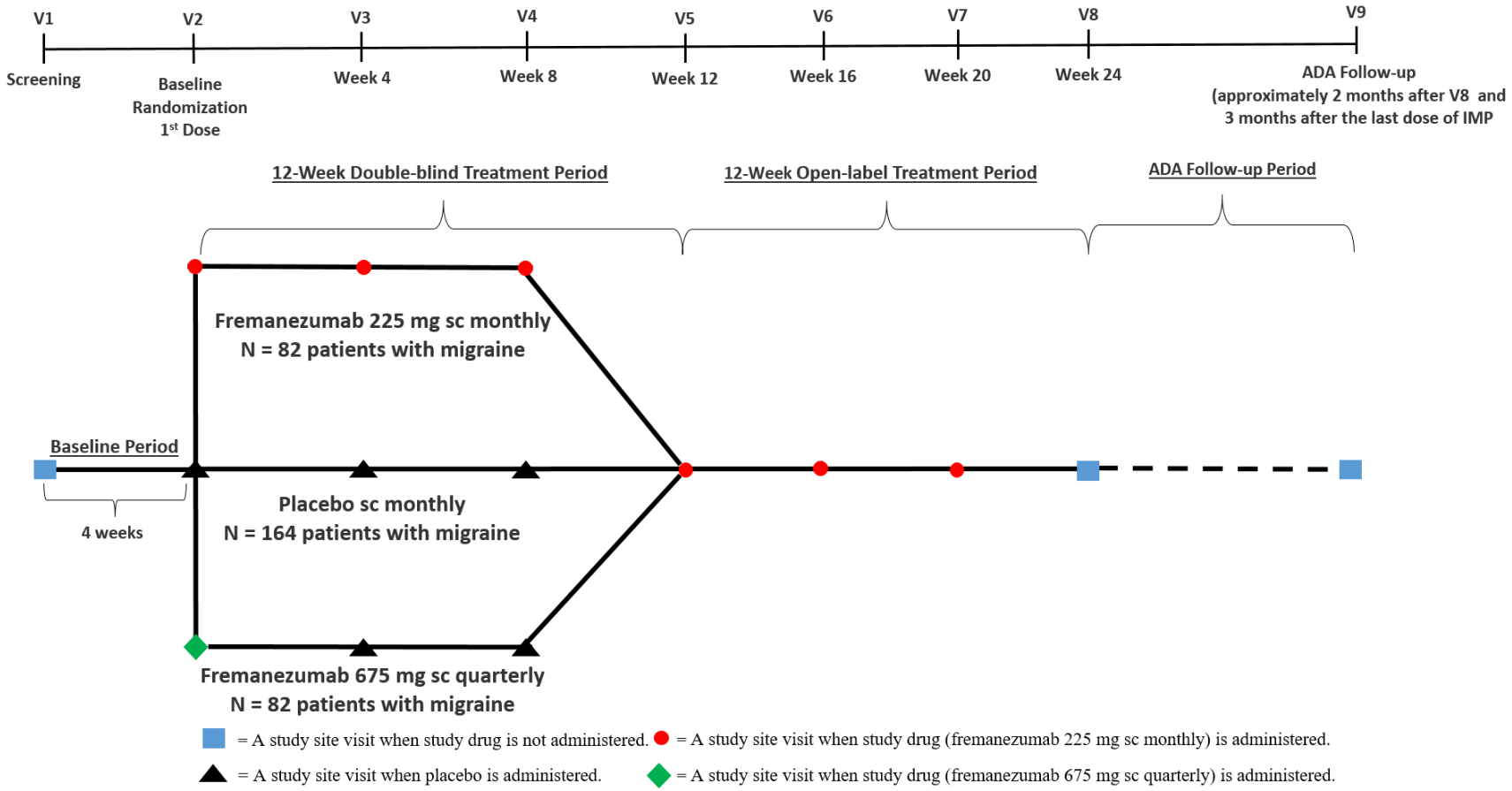
The end of study is defined as the last visit of the last patient (follow-up visit, visit 9). Two interim analyses are planned. The first interim database lock will occur following the end of the double-blind treatment period of the last patient for analysis of that portion of the study data (visit 5). A second interim database lock will occur following the end of the open-label period (visit 8). Final database lock will occur following the end of the follow-up period (visit 9). Following the first interim database lock, efficacy data from this period will not change but certain safety data may be updated to allow subsequent information to be added, eg. stop date,

outcome and action taken for study drug for adverse events and end date/ongoing for concomitant medications.

Study procedures and assessments with their timing are summarized in Table 3 of the study protocol. The study schematic diagram is shown in Figure 1.

In the event of a public health emergency, the investigational center will inform the patient of the safeguards being taken and will discuss their willingness or feasibility to come to the site for upcoming visits. If an ongoing patient cannot go to the site, the Medical Monitor will be notified to discuss further plans for that patient.

Figure 1: Overall Study Schematic Diagram



ADA=antidrug antibody; IMP=investigational medicinal product; N=planned number of patients in the study population; sc=subcutaneous; V=visit.
Note: Blood samples for plasma drug concentration will be collected at visits 2, 3, and 4. Patients will be asked to return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits to measure plasma fremanezumab concentration (one being 3 to 10 days after either visit 2, visit 3, or visit 4 and the other being 15 to 20 days after either visit 2, visit 3, or visit 4). If 2 additional visits are not possible for the patient, then the patient must return for only 1 additional pharmacokinetic blood sampling at either of the aforementioned time points. When patients return to the study center for additional blood sampling, then inquiries about adverse events and concomitant medications will be performed.

2.2. Randomization and Blinding

After the 28-day baseline period, the next 12 weeks of the study will be double-blind. Patients and investigators will remain blinded to IMP assignment during this double-blind period. This will be followed by a 12-week open-label period.

A computer-generated master randomization list will be provided to drug packaging facilities. The packaging vendor(s) will package the active IMP and placebo each into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance, and each will contain 1 prefilled syringe with either active IMP or placebo. Kits will be administered at each dosing visit as specified in the study protocol.

Patients will be stratified based on migraine type (CM vs EM) and baseline preventive medication use. Patients will be randomly assigned to treatment groups by means of a computer-generated randomization list using electronic IRT. This system is used to ensure a balance across treatment groups. The specifications for randomization will be under the responsibility and oversight of Teva Global Statistics.

At visit 2 (day 1), patients will be randomized in a 1:1:2 ratio within the appropriate stratum to 1 of 3 treatment groups, as assigned by the IRT:

- fremanezumab 225 mg sc once a month (approximately every 4 weeks), for a total of 3 doses; one 225 mg injection and 2 placebo injections at visit 2 and one 225 mg injection at visits 3 and 4
- fremanezumab 675 mg sc once a quarter (once at the beginning of the 12-week double-blind treatment period), for a total of 1 dose; three 225 mg injections at visit 2 and 1 placebo injection at visits 3 and 4 or
- placebo sc once a month (approximately every 4 weeks), for a total of 3 doses; 3 placebo injections at visit 2 and 1 placebo injection at visits 3 and 4

The placebo will contain the same vehicle and excipients as those for the active injection.

In the open-label extension phase starting at week 12, all patients will receive active treatment with a monthly dose of 225 mg sc fremanezumab.

The IRT will manage the initial drug supply, maintenance of adequate study drug supplies on site, and study randomization centrally. At the time of each study visit when the study drug is administered, the IRT will be queried, and the site personnel will retrieve the study drug from refrigerated storage and will administer a 1.5 mL volume from each syringe contained in the appropriately numbered kit(s).

The sponsor’s clinical personnel (and delegates) involved in the study will be blinded to the identity of the IMPs until the database is locked for analysis and the IMP assignment is known.

In the event of an emergency, it will be possible to determine to which treatment group the patient has been allocated by accessing the IRT system. All investigational centers will be provided with details on how to access the system for code breaking at the start of the study. The medical monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents.

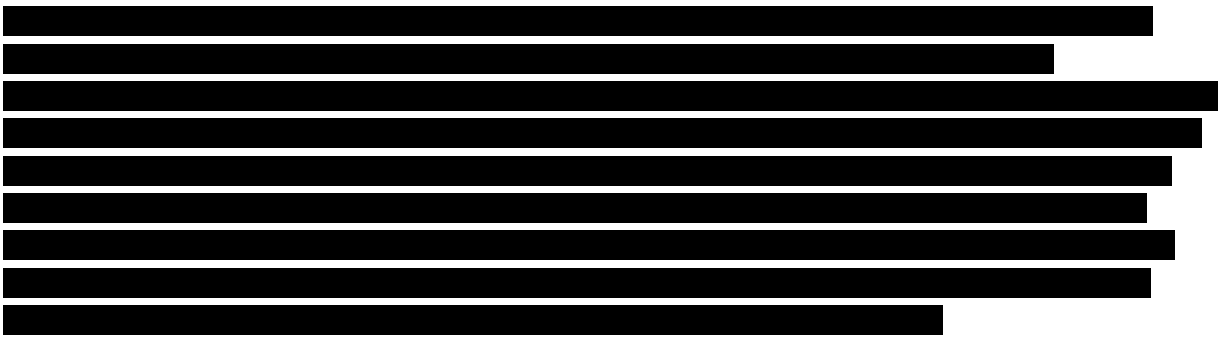
The randomization list will be assigned to the relevant treatment groups through a qualified service provider, eg, via the IRT system. The generation of the randomization list and the management of the IRT system will be done by a qualified service provider under the oversight of the responsible function at Teva.

2.3. Data Monitoring Committee

There will be no Data Monitoring Committee/Data and Safety Monitoring Board in this study.

2.4. Sample Size and Power Considerations

Using study data from 2 completed Phase 3 US pivotal studies in migraine, it is estimated that 163 completers per treatment group (ie, combined fremanezumab groups and placebo group) will provide at least 90% power to detect the assumed treatment difference at a significance level of 0.05. Assuming a 12% discontinuation rate, approximately 372 patients will be randomized in this study (93 patients in each fremanezumab treatment group and 186 patients in the placebo group). The primary efficacy analysis will consider all fremanezumab-treated patients as 1 group.



To ensure adequate representation of patients with both migraine types (EM and CM), the enrollment minimum of either migraine type is 30%. In addition, primary efficacy analysis will be stratified by EM and CM, and subgroup analysis for EM and CM will be conducted.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period. At this point, the study will be unblinded and an analysis of the double-blind period data performed. A second interim analysis is planned following the end of the open-label period.

The inferential analysis of efficacy variables for comparison between the fremanezumab treatment group (monthly dose and quarterly dose combined) and placebo applies only to the double-blind portion of the study, and will be conducted at the time of the first interim lock. Type 1 error control, as specified in Section 7 , applies only to the double-blind portion of the study.

Efficacy analysis after the 1st interim, which is the open label portion of the study, is considered exploratory and descriptive. This analysis will be done at the time of the second database lock.

2.5.2. Final Analyses and Reporting

All analyses identified in this SAP will be performed after the first interim database lock (at the end of the double-blind period) and after the second interim database lock (at the end of the open-label period) of this study. A final safety analysis will take place after the end of study as defined in the study protocol.

This SAP and any corresponding amendments will be approved before database lock, in accordance to GSD-SOP-702 (Statistical Analysis Plan).

The randomization codes will not be unblinded until this SAP has been approved and issued.

3. ANALYSIS SETS

3.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

3.2. Modified Intent-to-Treat Analysis Sets

The double-blind modified intent-to-treat (mITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP and have at least 10 days of post baseline efficacy assessment on the primary endpoint. The double-blind mITT analysis set will be used for the primary estimand analysis and all of its sensitivity analyses. The open-label mITT analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP during the open-label treatment period and have at least 10 days of post baseline diary entries during the open-label treatment period.

In the mITT analysis sets, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

3.3. Safety Analysis Sets

The double-blind safety analysis set will include all randomized patients who receive at least 1 dose of IMP during the double-blind treatment period. The open-label safety analysis set will include all patients who receive at least 1 dose of IMP during the open-label treatment period.

In the safety analysis sets, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized.

3.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the double-blind mITT analysis set including only patients without important deviations such as important inclusion/exclusion criteria deviations or any important deviations or omissions of the IMP administration. In the PP analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized. Patients with less than 75% diary compliance during the double-blind treatment period will be excluded from the PP analysis set. Patients who received study drug different from the study drug they were randomized to will be excluded from the PP analysis set. A blinded data review meeting will be conducted prior to the first interim database lock in order to determine the exclusion of the patients from the PP analysis set.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages; missing categories will be displayed as appropriate.

Data collected at the follow-up visit (visit 9) will be listed only.

4.2. Specification of Baseline Values

Patients will complete electronic headache diary entries daily for the 28-day run-in period, subjectively rating their headaches as mild, moderate, or severe and enter headache information about the previous day into the electronic headache diary device. If the run-in period is greater or less than 28 days, the baseline values for calculating the change from baseline of the monthly values of the efficacy variables will be prorated to **28** days.

The efficacy baseline values during the 28-day run-in period derived from the electronic headache diary device include

- total number of migraine days
- total number of days of use of any acute headache medications (as collected in the daily diary ie. in addition to randomized treatment)
- total number of headache days of at least moderate severity
- total number of headache days of any severity
- total number of headache hours of at least moderate severity
- total number of days with nausea or vomiting
- total number of days with photophobia and phonophobia
- total number of days of use of migraine-specific acute headache medications (triptans and ergot compounds)

Otherwise baseline value will be the last non-missing value prior to the 1st dose of study drug, unless otherwise noted.

4.3. Handling Withdrawals and Missing Data

If a patient has ≥10 days of electronic headache diary data after the 1st dose of the study drug, his/her monthly average number of days/hours of efficacy variables ***during the 12-week double blind period*** will be prorated to **28** days. Similarly, if a patient has ≥10 days of electronic headache diary data after the 4th dose of the study drug, his/her monthly average number of days/hours of efficacy variables ***during the 12-week open label period*** will be prorated to **28** days.

Patients who have <10 days of electronic headache diary data for the primary endpoint during the double blind period will be excluded from the double blind mITT analysis set. Patients who

have <10 days of electronic headache diary data during the open label period will be excluded from the open label mITT analysis set.

A patient's monthly number of days of efficacy variables ***during the 4-week period*** after each dose of study drug will be calculated. If a patient has missing diary days in a month, the following method will be used to handle the missing data.

- If the patient has 10 or more days of electronic headache diary data for a month, the monthly number of days/hours of efficacy variables will be prorated to **28** days for that month.
- If the patient has less than 10 days of electronic headache diary data for a month, the monthly number of days/hours of efficacy variables will be considered as missing.

A sensitivity analysis will be performed to assess the primary estimand using mixed-effects model for repeated measures (MMRM) as a different missing data handling approach. The methods will be described in detail in Section 6.2.3.1.

Multiple imputation (MI) method will be applied on the primary variable as sensitivity analyses. The methods will be described in detail in Section 6.2.3.2.

4.4. Study Days and Visits

Study days will be numbered relative to the 1st day of study drug administration. The start of treatment (visit 2 or day 1) is defined as the date on which a patient takes the 1st dose of study drug, as recorded on the study drug administration case report form (CRF). Days will be numbered relative to study drug start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

The 4-week (28-day) visit windows for the electronic headache diary device efficacy endpoints will be determined based on the actual dosing day. The run-in phase is defined as day -28 to -1 before the 1st injection on day 1. The 4-week period after the 1st dose of IMP is from the beginning of the 1st injection of study drug to just before the 2nd dose at visit 3/day 28. The 12-week double-blind treatment period is from the beginning of the 1st injection of study drug to just before the 4th dose at visit 5/day 84. The 12-week open-label treatment period is from the 4th injection of study drug on visit 5/day 85 to just before the 7th dose at visit 8/day 168 or the end of treatment visit. The follow-up period lasting 3 months after the last dose of IMP is from visit 8/day 169 to visit 9/day 224 or the end of study visit. Throughout this document, all by month efficacy summaries for the headache data will refer to these visit windows. If the Month 2, 3, 4, 5, 6 or 7 dosing day is missed, then the dosing day is considered to be previous dosing day +28 days. For all by-visit summaries, if there are multiple assessments at a postbaseline visit then the last non-missing assessment at that visit will be used for the summary. This includes assessments at the scheduled and unscheduled visits.

Unless otherwise stated, Last Assessment for summaries is the last observed postbaseline data. For patients who withdraw from the study, data at the early termination visit will be excluded from the by-visit summaries but will be included in the Last Assessment summaries.

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries unless otherwise specified. Summaries will be presented by migraine classification (ie, CM, EM, and all), treatment group, all fremanezumab and for all patients. Study population data will also be listed.

For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

5.2. Patient Disposition

Data from patients screened; patients screened but not randomized and reason for not being randomized will be summarized only for the overall group using patient counts.

Patients randomized (ie. ITT analysis set); patients randomized but not treated; patients in the double-blind mITT, double-blind safety, and PP analysis sets; reasons for exclusion from the PP analysis set, patients who complete the double-blind IMP; and patients who discontinue the double-blind IMP (including reason for discontinuation) will be summarized using descriptive statistics. Data from patients who discontinue the double-blind IMP will also be summarized by reason for withdrawal using descriptive statistics. Patients in the open-label mITT and the open-label safety analysis sets, reason for discontinuation from open-label treatment, reason for discontinuation from the study and patients who complete the study will also be summarized. The denominator for calculating the percentages will be the number of patients in the ITT analysis set.

5.3. Demographics and Baseline Characteristics

Patient demographic and baseline characteristics, including date of birth, age, ethnicity, race, sex, weight, height, body mass index, preventive medication use, time since initial migraine diagnosis, migraine classification (CM or EM), triptans/ergots use during baseline, migraine with aura, and ECG findings, will be examined to assess the comparability of the treatment groups and will be summarized using descriptive statistics. Categories for missing data will be presented if necessary.

The baseline electronic headache diary device efficacy variables will be summarized.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher. The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Patients are counted only once in each PT and SOC category. Summaries will be presented by treatment group and for all patients.

5.5. Prior Therapy and Medication

Any prior therapy, medication, or procedure a patient has had before study drug administration (ie, procedures for the treatment of migraine [eg, nerve blocks]) a patient has had within 6 months before study drug administration and preventive medications taken within 10 years) will be recorded on the CRF. Trade name or international nonproprietary name (INN), indication, and dosage will be recorded. The sponsor will encode all therapy and medication according to the World Health Organization (WHO) drug dictionary (WHODrug) version 2023MAR01DDE or higher.

Details regarding excluded prior medications, including preventive migraine treatments, are described in the exclusion criteria in the study protocol.

The incidence of prior therapies and medications will be listed by double-blind treatment group and summarized using descriptive statistics by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Prior therapies and medications will include all medications taken and therapies administered before the 1st day of study drug administration.

The prior medications will also be summarized for the following categories:

- butalbital for migraine/headache
- ergots for migraine/headache
- non-steroidal anti-inflammatory drugs (NSAIDs) for migraine/headache
- NSAIDs for other reason than migraine/headache
- opioids for migraine/headache
- opioids for reasons other reason than migraine/headache
- preventive medication from protocol Appendix K for migraine/headache
- preventive medication from protocol Appendix K for other reason than migraine/headache
- triptans for migraine/headache

5.6. Childbearing Potential and Methods of Contraception

For female patients, information related to childbearing potential, and menopause will be collected and listed.

For female and male patients, methods of contraception will be collected and listed.

5.7. Study Protocol Violations

Protocol deviations (PD) will be collected and reviewed by the study team prior to database lock and will be provided in a data listing. Patients with at least 1 important PD will be summarized for each category using descriptive statistics.

6. EFFICACY ANALYSIS

6.1. General

For the purposes of this study;

- CM is defined as headache occurring on ≥15 days during the screening period.
- EM is defined as headache occurring on <15 days during the screening period.

All e-diary data collected during the screening period, regardless of the duration beyond 28 days (e.g., 30 days), will be included and analyzed. There will be no exclusion of any e-diary data during the screening period.

A migraine day is endorsed when at least one of the following situations occurs:

- A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache meeting the criteria for migraine with or without aura
- A calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of a headache meeting the criteria for probable migraine, a migraine subtype where only 1 migraine criterion is missing
- A calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific medications (triptans and ergot compounds)

A headache day of at least moderate severity is endorsed when at least 1 of the following situations occurs:

- a calendar day (0:00 to 23:59) demonstrating at least 2 consecutive hours of headache of at least moderate severity
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds)

The derivation logic for both migraine day and headache day of at least moderate severity is presented in Appendix B.

In addition, a headache day of any severity is endorsed when at least 1 of the following situations occurs:

- a calendar day (00:00 to 23:59) demonstrating at least 2 consecutive hours of headache of any severity
- a calendar day (0:00 to 23:59) demonstrating a headache of any duration that was treated with migraine-specific acute medications (triptans and ergot compounds)

The endpoint of headache hours of at least moderate severity is obtained directly from the corresponding electronic headache diary device question (Question A5).

The endpoint of days of use of any acute headache medication is obtained directly from the corresponding electronic headache diary device questions (Question C1=Yes or C3=Yes and C2 has a medication present).

The endpoint of days of use of migraine specific acute medications (triptans and ergot compounds) is obtained directly from the electronic headache diary device question where Question C1=Yes and C2=ergot or triptan.

Other efficacy variables (days with nausea or vomiting, days with photophobia and phonophobia) will be derived using the e-diary data collected through the corresponding headache diary questions which can be found in Appendix A.

Patient satisfaction is measured by the PGIC scale which is a validated generic tool for the assessment of overall change in the severity of illness following treatment. Patients will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this study on a 7-point scale, where 1=no change (or condition got worse); 2=almost the same, hardly any change at all; 3=a little better but no noticeable change; 4=somewhat better, but the change has not made any real difference; 5=moderately better and a slight but noticeable change; 6=better and a definite improvement that has made a real and worthwhile difference; and 7=a great deal better and a considerable improvement that has made all the difference.

Based on the PGIC assessment, a dichotomous scale of "Yes" or "No" will be derived. A favorable change is score of 5-7 = 'Yes', which means there is significant improvement with the treatment. If the response is 1-4 = 'No', it is considered no significant change.

The ***monthly average number of days or hours*** of efficacy variables (eg, migraine days, days of headache with at least moderate severity, days of headache with any severity, total hours of headache with at least moderate severity, days of use of any acute headache medications, days with nausea or vomiting, days with photophobia and phonophobia, days of use of migraine-specific acute headache medications (triptans and ergot compounds) ***during the 12-week double-blind period*** after the 1st dose of study drug and ***during the 12-week open-label period*** after the 4th dose of study drug will be derived and prorated to **28** days equivalent using the following formula.

$$\frac{\sum Days\ of\ efficacy\ variable\ over\ the\ 12\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 12\ week\ period} \times 28 \quad (1)$$

The ***monthly number of days or hours*** of efficacy variables ***during the 4-week double-blind period*** after the 1st dose of study drug and ***during the 4-week open-label period*** after the 4th dose of study drug will be derived and prorated to **28** days equivalent using the following formula.

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ 4\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 4\ week\ period} \times 28 \quad (2)$$

Formula (2) will also be used for the variables ***during the 4-week period*** after each dose for months 1, 2, and 3 used in the sensitivity analysis for the primary estimand.

The ***baseline values*** will be calculated using all data collected in the run-in period and will be derived and prorated to **28** days equivalent using the following formula.

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ run-in\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ run-in\ period} \times 28 \quad (3)$$

The ***percentage of reduction*** in the monthly average number of an efficacy variable will be calculated as

$$\frac{baseline\ value - postbaseline\ value}{baseline\ value} \times 100\% \quad (4)$$

where the baseline value is calculated by formula (3) and the postbaseline value in the equation is calculated by formula (1) for the variables ***during the 12-week double-blind period or 12-week open-label period*** or by formula (2) for the variables ***during the 4-week double-blind period*** after 1st dose of study drug ***or the 4-week open-label period*** after 4th dose of study drug.

For the endpoints relating to a percentage reduction the patient is considered as a responder reaching 50%, 75%, or 100% reduction if the percent reduction in the efficacy variable as calculate by formula (4) is 50% or more, 75% or more, or 100% respectively. If a patient is early discontinued from the study, he/she will be counted as a non-responder.

Summaries will be presented by treatment group in the double-blind period for both the interim analysis at the end of the double-blind period and for the interim analysis at the end of the open-label period. There will be a column for placebo and a column for all fremanezumab-treated patients unless otherwise noted. Descriptive statistics for all efficacy data will be presented by-month over the 12-week period after the 1st dose of study drug for the first interim analysis and presented by-month over the 12-week period after the 4th dose of study drug for the second interim analysis.

The mITT analysis sets will be used for all efficacy analyses unless otherwise noted. As randomized stratification factors will be used for all relevant analyses unless otherwise noted. Summaries will be presented by treatment group as randomized, unless otherwise noted.

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Primary Estimand

The primary estimand will be the difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the double-blind mITT analysis set for the change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP. The intercurrent events (ICEs) that may affect the efficacy endpoint will be handled as per Table 1.

Table 1: Intercurrent Event Strategies: Primary Estimand

Intercurrent event	Strategy
Patient early terminates from the IMP	Treatment policy[1]
Patient receives the wrong IMP due to medication errors	Treatment policy[1]
Patient receives a rescue medication due to worsening symptoms	Treatment policy[1]

[1]Treatment policy: if observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

The baseline values will be derived using formula (3). The post baseline values will be derived using formula (1), and ***the change*** is calculated as ***postbaseline – baseline value.***

6.2.2. Primary Analysis of the Primary Estimand

The hypothesis testing for the primary analysis is:

$$H_o : \delta_1 = \delta_2 \quad vs \quad H_a : \delta_1 \neq \delta_2$$

where δ_1 and δ_2 are the parameters of mean change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP for the combined TEV-48125 treatment groups and the placebo group respectively.

An analysis of covariance (ANCOVA) will be performed, including treatment (combined TEV-48125 groups vs. placebo) and stratification factors (as randomized) of migraine type (CM vs EM) and baseline preventive medication use (yes vs no) as fixed factors, as well as baseline number of migraine days as a covariate in the model. For the individual treatment groups (combined TEV-48125 groups and placebo) the least square (LS) mean, standard error (SE) and corresponding 95% confidence interval will be presented. For the treatment difference (combined TEV-48125 groups - placebo) the LS mean, SE, corresponding 95% confidence interval and p-value for comparison will be presented.

The statistical test will be two-sided at the alpha = 0.05 level of significance. Model fitting assumptions will be investigated.

Example SAS code is provided in Appendix D.

A hierarchical procedure will be used to control the type 1 error rate, as described in Section 7 .

6.2.3. Sensitivity Analysis of the Primary Estimand

6.2.3.1. MMRM Analysis

The sensitivity of the primary analysis to missing data will be assessed using mixed-effects model for repeated measures (MMRM) via restricted maximum likelihood estimation and assuming a missing at random (MAR) mechanism.

Each patient's monthly number of migraine days ***during the 4-week period*** for month 1, month 2 and month 3 will be calculated by formula (2) in Section 6.1 based on the electronic headache diary device responses for that month. If a patient is early terminated or has intermittent missing days (ie. fewer than 10 days of electronic headache diary entries for a month), that month's value will be considered as missing as described in Section 4.3.

The model will include treatment, month and stratification factors of migraine type (CM vs EM) and baseline preventive medication (yes vs no) use as fixed factors and treatment-by-month interaction effects, and baseline number of migraine days as a covariate. Patient will be included in the repeated statement as a random effect. The unstructured covariance model will be used for repeated observations within patients. If the model does not converge, then simpler covariance structures with fewer parameters will be used: heterogeneous autoregressive (1), heterogeneous compound symmetry, autoregressive (1), and compound symmetry, and the

variance covariance structure which minimizes the Akaike's information criterion (AIC) will be selected.

The 12-week monthly average number of migraine days will be estimated by the LS means of the overall treatment effect over 3 months for each treatment group (combined TEV-48125 groups and placebo) along with SE and 95% confidence interval, and the LS means will be calculated for the treatment difference (combined TEV-48125 groups - placebo) along with SE, 95% confidence interval and nominal p-value. These calculations will be done by month as well as for the overall double-blind treatment period.

The LS means ±SE of monthly change from baseline values estimated by MMRM will be plotted by month for each treatment group.

Example SAS code is provided in Appendix D.

In addition, a further MMRM analysis will also be performed to examine the sensitivity of the statistical inferences against departure from the assumption of time-independent effect of baseline number of migraine days. The model will be the same as that above, but will include a time-by-baseline interaction along with baseline as a continuous covariate. Therefore the model will include the fixed categorical effects of treatment, month, stratification factors of migraine type (CM vs EM) and baseline preventive medication (yes vs no) and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline number of migraine days and baseline number of migraine days-by-month interaction. Example SAS code is provided in Appendix D.

6.2.3.2. Analysis with Multiple Imputation Method

Multiple imputation (MI) method will be applied to impute the monthly missing data assuming a missing not at random (MNAR) mechanism. The data will be processed by the following steps.

- If a patient has <10 days of electronic headache diary device data in a month, that month's value will be considered missing before the MI procedure.
- For the patients in the active treatment groups who are early terminated with reasons of treatment-related adverse event or lack of efficacy, they will be assigned to placebo group so their missing values will be imputed using data from the placebo treated patients.
- Run SAS PROC MI procedure to create 100 complete datasets.
- Within each imputed data set, for a patient who has partial, say X days (X<28), electronic headache diary device data in a month, the monthly value will be replaced by $\sum(oberseved\ migraine\ days\ ) + (28 - X) * imputed\ value/28$
- The monthly average number of migraine days ***during the 12-week period*** after the 1st dose of study drug will be the average of month 1, month 2, and month 3 values.

Each dataset will be analyzed using the same ANCOVA model as described in Section 6.2.2. The LS means and standard errors from each analysis will be output to a SAS data set. SAS MIANALYZE procedure will be used to generate the final LS means (±SE) for the treatment groups and the treatment difference (TEV-48125 - placebo) as well as p-values associated with

treatment differences. The 95% confidence intervals for the treatment difference will also be constructed.

The output dataset will contain the estimate of the mean difference and the standard error of the estimate from each of the 100 datasets. SAS procedure, PROC MIANALYZE, will be used to generate an overall p-value and 95% CI for the treatment difference.

This sensitivity analysis will be performed on the ITT analysis set.

Example SAS code is provided in Appendix D.

6.2.3.3. ANCOVA Analysis using Actual Stratification Factors

The primary ANCOVA analysis will be repeated as a sensitivity analysis using the actual stratification factors in the model. This sensitivity analysis will be performed on the double-blind mITT analysis set.

6.2.3.4. Analysis Split by Treatment Regimen Group

A sensitivity analysis will be performed on the primary estimand to assess the sensitivity of the analysis to treatment regimen. This analysis will be identical to the primary analysis but where the two fremanezumab treated groups will be presented separately. The columns will be placebo, TEV-48125 225 mg monthly and TEV-48125 675 mg quarterly and the treatment comparisons will be TEV-48125 225 mg monthly – placebo and TEV-48125 675 mg quarterly – placebo. For both the individual treatment groups and the treatment comparisons the LS mean, SE and corresponding 95% confidence interval will be presented. No p-values will be presented for this additional analysis.

6.2.4. Supplementary Estimands

A supplementary estimand will estimate treatment effect in the hypothetical scenario where no one early terminates from study drug. The estimand is the difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the double-blind mITT analysis set for the change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP where the ICEs are handled as per Table 2.

Table 2: Intercurrent Event Strategies: 1st Supplementary Estimand

Intercurrent event	Strategy
Patient early terminates from the IMP	Hypothetical: For patients in the monthly dosing regimen group who early terminate from study drugs, observations collected more than 4 weeks after the last dose will be treated as missing. In formula (1) an average is taken so these values which are left missing due to early termination will be replaced with the average for that month of those in the same treatment group who do not early terminate. Missing observations prior to early termination will not be replaced.
Patient receives the wrong IMP due to medication errors	Treatment policy[1]

Intercurrent event	Strategy
Patient receives a rescue medication due to worsening symptoms	Treatment policy[1]

[1]Treatment policy: if observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

A second supplementary estimand will estimate treatment effect in the hypothetical scenario where no one takes rescue medication (rescue medication is indicated by a response of Yes to C1 or C3, and a medication present in response to C2 of the electronic headache diary device). A rescue medication for migraine is defined as medication that does not abort a migraine, but masks the pain for a few hours until the migraine runs its course.

The estimand is the difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the double-blind mITT analysis set for the change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP where the ICEs are handled as per Table 3.

Table 3: Intercurrent Event Strategies: 2nd Supplementary Estimand

Intercurrent event	Strategy
Patient early terminates from the IMP	Treatment policy[1]
Patient receives the wrong IMP due to medication errors	Treatment policy[1]
Patient receives a rescue medication due to worsening symptoms	Hypothetical: For patients who start a rescue medication, observations collected after starting rescue medication will be treated as missing. In formula (1) an average is taken so these values which are left missing due to starting rescue medication will be replaced with the average for that month of those in the same treatment group who do not start rescue medication.

[1]Treatment policy: if observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

A third supplementary estimand will estimate treatment effect in the population that comprises the patients in the ITT analysis set. The estimand is the difference in adjusted means between fremanezumab group and placebo group for the change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP where the ICEs are handled as per Table 1.

Finally, a fourth supplementary estimand will estimate the treatment effect in the population that comprises the patients in the PP analysis set. The estimand is the difference in adjusted means between fremanezumab group and placebo group for the change from baseline in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP where the relevant ICE is handled as per Table 4.

Table 4: Intercurrent Event Strategies: 4thSupplementary Estimand

Intercurrent event	Strategy
Patient receives a rescue medication due to worsening symptoms	Treatment policy[1]

[1]Treatment policy: if observations are collected after the occurrences of the ICEs, the observations will be included in the calculation of the primary endpoint for the primary analysis.

6.2.5. Analysis of the Supplementary Estimands

The supplementary estimands will be analyzed using the same methods as the primary estimand, as detailed in Section 6.2.2.

6.2.6. Sub-Group Analyses

The primary analysis with ANCOVA method defined in Section 6.2.2 and MMRM analysis defined in Section 6.2.3.1 will also be applied to the following subgroups for the primary endpoint using a 'by' statement with the subgroup variable of interest. The subgroup variable will not be included in the model. Instead of the randomized stratification, the actual stratification will be used.

- Patients by migraine type (CM, EM)

6.3. Secondary Efficacy Endpoints and Analysis

6.3.1. Secondary Efficacy Estimands

The secondary estimands are as follows:

- The difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the mITT analysis set for the change from baseline in the number of migraine days during the 4-week period after the 1st dose of investigational medicinal product (IMP).
- The difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the mITT analysis set for the change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP.
- The odds ratio of fremanezumab group with placebo group in the population that comprises the patients in the mITT analysis set n for the proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP.
- The difference in adjusted means between fremanezumab group and placebo group in the population that comprises the patients in the mITT analysis set for the change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP.

For all secondary estimands the ICEs will be handled as per Table 1.

For the first secondary efficacy estimand the baseline values will be derived using formula (3). The postbaseline values ***during the 4-week period*** will be derived using formula (2) and ***the change*** is calculated as ***postbaseline – baseline value.*** For the second and fourth secondary efficacy estimands the baseline values will be derived using formula (3). The postbaseline values ***during the 12-week period*** will be derived using formula (1), and ***the change*** is calculated as ***postbaseline – baseline value.***

For the third secondary efficacy estimand the ***percent reduction*** will be calculated using formula (4). If a patient is early discontinued from the study, he/she will be counted as a non-responder.

6.3.2. Analysis of Secondary Efficacy Estimands

The first, second, and fourth secondary efficacy estimands which involve the difference in means between fremanezumab group and placebo group for change from baseline in efficacy variables will be analyzed using the same methods as the primary efficacy endpoint as detailed in Section 6.2.2 and 6.2.3.1 except the second secondary efficacy estimand model will include baseline number of days that any acute headache medications were used instead of baseline number of migraine days and the fourth secondary efficacy estimand model will include baseline number of days with headache of at least moderate severity instead of baseline number of migraine days.

The third secondary efficacy estimand involving the responder endpoint will be analyzed using logistic regression. The model will include treatment and stratification factors of migraine type (CM vs EM) and baseline preventive medication (yes vs no) use as fixed factors, as well as baseline number of migraine days as a covariate in the model. For the individual treatment groups (combined TEV-48125 groups and placebo) number and percent of responders and non-responders will be presented. For the treatment comparison (combined TEV-48125 groups with placebo) the odds ratio, 95% confidence interval for the odds ratio, and p-value for the treatment comparison will be presented.

Example SAS code is provided in Appendix D.

6.3.3. Supplementary Secondary Efficacy Estimands

The supplementary secondary efficacy estimands are identical to the secondary efficacy estimands but in the per-protocol (PP) analysis set. See Section 6.3.1 for the secondary efficacy estimands.

6.3.4. Analysis of Supplementary Secondary Efficacy Estimands

The analysis of the supplementary secondary efficacy estimands will be identical to the analysis of the secondary efficacy estimands. See Section 6.3.2 for details.

6.4. Other Efficacy Endpoints and Analysis

6.4.1. Exploratory Efficacy Endpoints

[redacted]

[redacted]

[redacted]

6.4.2. Analysis of Exploratory Endpoints

[redacted]

7. MULTIPLE COMPARISONS AND MULTIPLICITY

A fixed-sequence, hierarchical testing procedure will be implemented to control the type 1 error rate at 0.05 for formal hypothesis testing of the secondary endpoints at the end of the double-blind period (i.e., 1st interim). Upon the success of the primary analysis, the first secondary endpoint in the sequence will be tested at a significance level of 0.05, and a p-value ≤0.05 will be interpreted inferentially. The process will continue following the order of the sequence until a point when the test for the efficacy endpoint fails, ie, 2-sided p-value >0.05. Subsequently, no further test results will be interpreted inferentially. The sequence of testing upon the success of the primary analysis will be as follows:

1. mean change from baseline in the number of migraine days during the 4-week period after the 1st dose of IMP
2. mean change from baseline in the monthly average number of days with headache of at least moderate severity during the 12-week period after the 1st dose of IMP
3. proportion of patients reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the 1st dose of IMP
4. mean change from baseline in the monthly average number of days that any acute headache medications were used during the 12-week period after the 1st dose of IMP

8. SAFETY ANALYSIS

8.1. General

Safety analyses will be performed on the safety analysis set. Summaries will be presented by treatment group in double-blind period for both the interim analysis at the end of the double-blind period and for the interim analysis at the end of the open-label period (TEV-48125 225 mg monthly, TEV-48125 675 mg quarterly and placebo). A column for all fremanezumab-treated patients will be provided and a total column will also be provided.

For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided.

Missing values will be reported as missing and no imputation will be undertaken.

All data during the follow-up period, i.e., after the open-label period, will be listed only.

8.2. Duration of Exposure to Study Drug

Duration of treatment (days treated) for the double-blind treatment period is the number of days on treatment starting from the 1st study drug administration day to the week 12 or double-blind early withdrawal visit day (week 12 or double-blind early withdrawal visit day – first day of study drug + 1). For patients who are lost to follow-up during the double-blind treatment period, the EOT visit date is defined as the last study drug administration + 27.

Duration of treatment (days treated) for the open-label treatment period is the number of days on treatment starting from the 1st study drug administration day in the open-label treatment period to the week 24 or open-label early withdrawal visit day (week 24 or open-label early withdrawal visit day – first day of study drug in the open-label treatment period + 1). For patients who are lost to follow-up during the open-label treatment period, the EOT visit date is defined as the last study drug administration + 27.

Duration of treatment (days) during the double-blind and open-label periods will be summarized using descriptive statistics.

8.3. Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or higher.

For adverse event recording, the study period is defined for each patient as the time period from signature of the informed consent form to the end of the follow-up period. Adverse events will be presented separately for the double-blind period and for the open-label period.

Adverse events will be collected at each visit via adverse event inquiry.

The following are considered protocol-defined adverse events of special interest to be sent to the sponsor's Global Patient Safety and Pharmacovigilance for evaluation: severe hypersensitivity and anaphylaxis, as well as ophthalmic events of at least moderate severity.

Summaries will be presented by migraine classification for all treatment-emergent adverse events (overall and by severity), adverse events determined by the investigator to be treatment-related adverse events (ie, reasonable possibility; defined as related or with missing relationship [overall and by severity]), serious adverse events, protocol-defined adverse events of special interest, adverse events leading to discontinuation from treatment, adverse events leading to discontinuation from the study, non-serious adverse events, injection site reaction adverse events, adverse events requiring concomitant or additional treatment, and adverse events leading to death.

The incidence of adverse events will be summarized using descriptive statistics by migraine classification, PT and SOC. Each patient will be counted only once in each PT or SOC category for the analyses of safety. For the summaries by severity, patients are counted at the greatest severity. Adverse events with the missing flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events.

Listings for adverse events, deaths, serious adverse events, serious adverse events additional information, adverse events leading to discontinuation from treatment, adverse events leading to discontinuation from the study, injection site related adverse events requiring concomitant or additional treatment given, protocol-defined adverse events, protocol-defined adverse events of special interest, and adverse events for patients who did not meet screening criteria will be presented. All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, PT, SOC, date of onset, date of resolution, severity, and relationship to treatment. The onset of adverse events will also be shown relative (in number of days) to the 1st day of treatment. In addition, MedDRA dictionary terms for adverse event descriptions, and adverse event preferred terms by patient number and treatment group will be presented.

8.4. Deaths

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the clinical study report.

8.5. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis) will be performed using the central laboratory at the time points detailed in the study protocol. Specific laboratory tests to be performed are listed below in Table 5.

Table 5: Clinical Laboratory Tests

Serum chemistry	Hematology and coagulation	Urinalysis
Calcium	Hemoglobin	Protein
Phosphate	Hematocrit	Glucose
Sodium	Erythrocytes	Ketones
Potassium	Platelets	Hemoglobin
Chloride	Leucocytes	pH
Creatinine	– Neutrophils	Specific gravity
Glucose	– Lymphocytes	Microscopic tests
BUN	– Eosinophils	– Bacteria
LDL	– Monocytes	– Erythrocytes
HDL	– Basophils	– Leucocytes
Triglycerides	Lymphocytes atypical	– Crystals
Urate	Prothrombin INR	– Casts
ALT		
AST		
LDH		
GGT		
ALP		
Bicarbonate		
Carbon dioxide		
Protein		
Albumin		
Bilirubin		
Direct bilirubin		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyl transpeptidase; HDL=high-density lipoprotein; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low-density lipoprotein.

Laboratory test results will be presented in standard international (SI) units.

Summary statistics for chemistry, hematology, urinalysis, and coagulation laboratory tests will be presented at baseline, weeks 0, 8, 12 for double-blind and week 24 for open-label, and last on study assessment for both periods. Laboratory values and changes from baseline to each visit and last on study assessment will be summarized using descriptive statistics. Shifts (below, within, and above the normal range) from baseline to each visit and last on study assessment will be summarized using patient counts. Listings of all individual patients' laboratory test results will be presented.

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded both on the source documentation and the CRF as an adverse event. The incidence of potentially

clinically significant abnormal results will be summarized using descriptive statistics with the criteria specified in Table 6. The potentially clinically significant abnormal laboratory values will include all postbaseline values (including scheduled, unscheduled, and early termination visits) for the summaries. Listings of patients who have potentially clinically significant abnormal laboratory data will be presented.

Table 6: Criteria for Potentially Clinically Significant Laboratory Values

Test		Criterion value
Serum chemistry		
Alanine aminotransferase (ALT)		≥3x ULN
Aspartate aminotransferase (AST)		≥3x ULN
Alkaline phosphatase		≥3x ULN
Gamma-glutamyl transpeptidase (GGT)		≥3x ULN
Lactate dehydrogenase (LDH)		≥3x ULN
Blood urea nitrogen (BUN)		≥10.71 mmol/L
Creatinine		≥177 μmol/L
Uric acid	Men	≥625 μmol/L
	Women	≥506 μmol/L
Bilirubin (total)		≥ 2x ULN
Potassium		≤3 mmol/L or ≥6 mmol/L
Calcium		≤1.5 mmol/L or ≥3.5 mmol/L
Hematology and Coagulation		
Hematocrit	Men	<0.37 L/L
	Women	<0.32 L/L
Hemoglobin	Men	≤115 g/L
	Women	≤95 g/L
White blood cell (WBC) counts		≤3 x 10^9/L ≥20 x 10^9/L
Eosinophils		≥10%
Absolute neutrophil counts (ANC)		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L ≥700 x 10^9/L
INR		≥ 1.5x ULN
Urinalysis		
Blood (HGB)		≥2 unit increase from baseline
Glucose		≥2 unit increase from baseline
Ketones		≥2 unit increase from baseline
Total protein		≥2 unit increase from baseline

HGB=Hemoglobin; INR=International Normalized Ratio; ULN=upper limit of normal range.

8.5.1. Laboratory Values Meeting Hy's Law Criteria

All occurrences of possible drug-induced liver injury that meet Hy's law criteria as defined in the protocol will be included in adverse events reporting.

8.5.2. Other Clinical Laboratory Tests

8.5.2.1. Human Chorionic Gonadotropin Test

Serum beta-human chorionic gonadotropin (β-HCG) tests will be performed for all women of childbearing potential at screening (visit 1) and visit 8. Urine pregnancy tests will be performed for all women of childbearing potential at visit 2 to 7 and the EOT/early termination visit. Pregnancy test results will be listed.

8.5.2.2. Follicle-Stimulating Hormone Test

Postmenopausal women will have a follicle-stimulating hormone (FSH) test at screening. Results will be listed.

8.6. Physical Examinations

Physical examinations, including height (to be measured at the screening visit only) and weight will be performed at screening, weeks 0, 4, 8, 12, 24 and last on study assessment.

A complete physical examination will include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Any physical examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event and recorded on the CRF, and monitored as described in the study protocol. Abnormal findings at baseline will be summarized by treatment group using patient counts. Shifts from baseline to weeks 4, 8, 12 for double-blind and week 24 for open-label and last on study assessment for both periods will be summarized using patient counts. Listings of findings for all physical examinations will be presented.

Descriptive statistics for weight and height will be provided.

8.7. Vital Signs

Vital signs (blood pressure [systolic/diastolic], respiratory rate, body temperature, and pulse) will be measured at every visit including unscheduled visits.

For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event.

Vital signs values and changes from baseline to each visit and endpoint will be summarized using descriptive statistics and vital signs values will be listed.

Table 7 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to be identified as potentially clinically significant abnormal, a value would need to meet both conditions below: i.e., have a value beyond the criterion value and a change of at least the magnitude specified in the change from baseline column. The

potentially clinically significant abnormal vital signs values will include all postbaseline values (including scheduled, unscheduled, and early termination visits) for the summaries. The incidence of potentially clinically significant values will be both listed and summarized using descriptive statistics.

Table 7: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15 bpm
	≤50 bpm	Decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤90 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15 mm Hg
	≤50 mm Hg	Decrease of ≥15 mm Hg
Respiratory rate	<10 breaths/min	
Body temperature	≥38.3°C	Change of ≥1.1°C

8.8. Electrocardiography

A single 12-lead ECG will be performed at screening, week 0, 8, 24, and at visit 9 (follow-up) if assessment at visit 8 (EOT/ET) shows abnormality. This procedure will be performed predose.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

If results are abnormal, the ECG will be repeated 1 time.

Summary of ECG findings (normal, abnormal not clinically significant and abnormal clinically significant) will be presented at baseline. Shifts in ECG finding (normal, abnormal not clinically significant and abnormal clinically significant) from baseline to overall result interpretation, week 8 for double-blind and week 24 for open-label and last on study assessment (double-blind and open-label) will be summarized using patient counts. For overall result interpretation the worst post baseline finding for the patient (the abnormal finding if there are both normal and abnormal findings) will be used in the summaries. Actual values and changes from baseline to each visit and last on study assessment (for both double-blind and open-label periods) will be summarized using descriptive statistics. Both result interpretation and values will be listed.

Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with the baseline value will be considered an adverse event.

8.9. Concomitant Medications or Therapies

Any concomitant therapy, medication or procedure up to the end of the study period will be recorded on the CRF. Generic or trade name, indication, and dosage will be recorded. The

sponsor will encode all therapy and medication according to the World Health Organization Drug Dictionary (WHODrug) version 2023MAR01DDE or higher.

Up to 30% of patients will be allowed to remain on stable doses of no more than 1 preventive migraine medication presented in the study protocol (in addition to other medications not listed in the study protocol) for the duration of the study. Patients on preventive medication must be on a stable dose for at least 2 months of consecutive use prior to screening with no expectation to change dosing regimen or change to another migraine preventive medications during the treatment phase of the study.

Patients will be allowed to use acute medication to treat breakthrough migraines as needed, with the exception of medications containing opioids and barbiturates, which cannot be used on more than 4 days during the screening period. Traditional Chinese therapy (including herbal medicine) and acupuncture are allowed if the patient is on a stable dosing regimen for at least 2 months (consecutive) before screening.

Concomitant medications will be listed by double-blind treatment group. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and PT. Patients are counted only once in each therapeutic class category, and only once in each PT category. Concomitant medications will include all medications taken while the patient is treated with the IMP.

The subset of concomitant pain medication and medication or therapy for migraine/headache will also be summarized by the following indication categories:

- butalbital for migraine/headache
- ergots for migraine/headache
- NSAIDs for migraine/headache
- NSAIDs for other reason than migraine/headache
- opioids for migraine/headache
- opioids for reasons other reason than migraine/headache
- preventive medication from protocol Appendix K for migraine/headache
- preventive medication from protocol Appendix K for other reason than migraine/headache
- triptans for migraine/headache

8.10. Suicidality

Any suicide attempt in the past, suicidal ideation with a specific plan in the past 2 years prior to screening (visit 1), or current suicidal ideation will result in patient exclusion.

Investigators will inquire about and evaluate suicidal ideation, plan, and behavior based on their clinical judgement and refer patients to psychiatric care as appropriate.

Any suicide information collected will be listed.

9. TOLERABILITY VARIABLES AND ANALYSIS

Spontaneous reports of injection site reactions will be recorded as adverse events according to the following severity assessment criteria:

- Spontaneous reports of injection site erythema, induration, and ecchymosis will be recorded according to measurements: 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe).
- Spontaneous report of local pain after the injection will be recorded as mild, moderate, or severe according to patient's self-report.
- Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Tolerability will be assessed by the following:

- the number (%) of patients who fail to complete the study due to adverse events

Spontaneously reported local tolerability findings will be listed and summarized descriptively.

10. PHARMACOKINETIC ANALYSIS

Pharmacokinetic plasma concentration results (fremanezumab) are collected at visit 2, visit 3, visit 4, and visit 8 and patients must return to the study center after visit 2, visit 3, or visit 4 for 2 additional blood sampling visits (see study protocol for details). Samples from patients who received the active IMP will be analyzed for the concentration of fremanezumab using a validated method. Samples from patients who were randomized to receive placebo will not be analyzed.

The plasma concentration results will be tabulated descriptively at each planned sampling time point by treatment group. Concentration values that are below the lower limit of quantitation (<LLOQ) will be treated as 0, and missing values will be ignored in the concentration summary tables. Individual pharmacokinetic concentration data will be summarized and listed in the CSR.

The pharmacokinetic data from this study will be pooled with the data from other fremanezumab studies and assessed for comparability. Summary statistics of fremanezumab pharmacokinetic parameters model-based predictions of weight-adjusted exposures will be compared and will be reported separately.

11. IMMUNOGENICITY ANALYSIS

Samples from patients who receive the active IMP will be analyzed for ADA using a validated method. Samples from patients who receive placebo will not be analyzed.

Blood samples (10 mL for the predose sample at visit 2; 6 mL for all other samples) will be collected prior to dosing at visit 2, visit 4, visit 8 (EOT), and visit 9 (EOS) for immunogenicity testing.

Summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. This analysis will be reported separately.

12. PLANNED INTERIM ANALYSES

Two interim analyses are planned. The first interim analysis is planned when the last patient has completed the double-blind period and will use the double-blind period data. A second interim analysis is planned following the end of the open-label period and will use the open-label period data.

The inferential analysis of efficacy variables for comparison between each fremanezumab treatment group (monthly dose and quarterly dose) and placebo will be done at the time of the first interim lock. The appropriate method for type 1 error control will be applied to the first interim analysis.

Efficacy analysis for the open-label portion of this study is considered exploratory and mainly descriptive. This analysis will be done at the time of the second database lock.

13. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

14. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

The following endpoint has been removed in the SAP due to the necessary data not being collected:

- mean change from baseline in the monthly average number of days with most bothersome symptoms during the 12-week period after the 1st dose of IMP

The wording of the following endpoint has been changed as shown.

Wording from protocol:

- mean change from baseline (day 0) of patient satisfaction, as measured by the PGIC scale, at 4 weeks after the last (6th) dose of study drug

New wording in SAP:

- assessment of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at visit 8

A multiple imputation analysis has been added in Section 6.2.3.2 as an additional sensitivity analysis of the primary estimand to assess the sensitivity of the primary analysis to missing data assuming the data is missing not at random.

The definitions for CM and EM have been modified; CM is defined as having ≥ 15 headache days during the baseline period whilst < 15 headache days during the baseline period is classed as EM.

The following analysis has been removed in the SAP due to minimal COVID-19 diagnoses occurring:

- Missing data or visits due to the COVID-19 pandemic will be evaluated for the primary and secondary endpoints. COVID-19 may have an impact on patients' migraine symptoms, with headache reported to be a common complication as a result of contracting the disease. All COVID-19 cases will be included in the primary analysis; however, observations following COVID-19 diagnosis will be discarded from the calculation of the monthly average endpoint. The data handling strategy will be detailed in the statistical analysis plan.

The following subgroup analysis has been removed in the SAP due to disease severity being collected daily rather than just once during the baseline period:

- Patients by disease severity (Mild, Moderate, Severe)

15. REFERENCES

Chinese Medical Association Pain Society (CMAPS). Guide to the prevention and treatment of migraine in China. Chin J Pain Med 2016;22:721-7.

Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1-211.

APPENDIX A. ELECTRONIC HEADACHE DIARY QUESTIONNAIRE

	The following questions are referring to yesterday (00:00 - 23:59)
A1	Did you have a headache yesterday?
A2	Did you have at least two (2) consecutive hours of headache yesterday?
A3	What was the greatest severity that your headache reached yesterday at any time?
A4	How many total hours did you have a headache of any severity yesterday?
A5	How many total hours of moderate or severe headache did you have yesterday?

	The following questions are referring to yesterday (00:00 - 23:59)
B1	Was your headache pain worse on one side (left or right) of your head yesterday?
B2	Was your head pain throbbing, pounding or beating like a drum yesterday?
B3	Did you have a stomach ache, feel sick to your stomach or did you throw up yesterday?
B4	Did light bother you more than when you didn't have a headache (did you experience photophobia)?
B5	Did sounds bother you more than when you didn't have a headache (did you experience phonophobia)?
B6	Did you have trouble seeing normally or did you see spots, stars, wavy lines, or flashes during your headache yesterday? (This is different from "light bothers you")
B7	Did you have feelings such as numbness or tingling in any part of your body or face around the time of your headache?
B8	Before your headache started, did you notice any of the usual signs that a headache is coming yesterday? This could include seeing spots, stars, wavy lines, or flashes or having trouble speaking, feeling dizzy or having tingling, numbness or weakness in your arms or legs.

	The following questions are referring to yesterday (00:00 - 23:59)
C1	Did you take any prescription medications yesterday for your headache/migraine?
C2	Which of these medications did you take yesterday?
C3	Did you use any non-prescription medication in an effort to get relief from your headache/migraine yesterday?

	The following questions are referring to yesterday (00:00 - 23:59)
E1	Did you have problems falling asleep yesterday?
E2	Which of the following situations best describe your work/school performance yesterday, when you did not have a headache?
E3	What would better describe how you felt in general yesterday?
E4	How much of the time yesterday did you find it difficult to concentrate on what you needed to do?
E5	On average, how much of the time yesterday were you very tired, asleep, or feeling drained?
E6	Which of the following situations best describe your ability to perform household chores yesterday, when you did not have a headache?
E7	How engaged were you with your partner's or children's activities yesterday, when you didn't have a headache?
E8	Overall, how interested were you in doing daily activities yesterday?

APPENDIX B. LOGICS FOR ENDPOINTS DERIVATION

Migraine day: 1 of the following 5 options
Primary endpoint

OPTION 1

Part 1	**1**	**A1**	YES
	2	**A2**	YES
		AND	
		ONE OF THE FOLLOWING	
Part 2	**1**	**A3**	Moderate/Severe
	2	**B1**	YES
	3	**B2**	YES
		AND	
		ONE OF THE FOLLOWING	
Part 3	**1**	**B3**	YES
	2	**B4**	YES
		AND	
		B5	YES

OPTION 2

1	**A1**	YES
2	**C1**	YES
3	**C2**	ERGOT OR TRIPTAN

OPTION 3

1	**A1**	YES
2	**C2**	Medication Provided
3	**C3**	YES

OPTION 4

1	**A1**	YES
	AND	
	ONE OF THE FOLLOWING	
2	**B6**	YES
	OR	
	B7	YES

OPTION 5: PROBABLE MIGRAINE

If **Part 1** and **Part 2** met from option 1, **Part 3** needs ONLY one of the following:

Part 3		**B4**	YES
		B5	YES

If **Part 1** and **Part 3** met from option 1, **Part 2** needs ONLY one of the following:

Part 2	**1**	**A3**	Moderate/Severe
	2	**B1**	YES
	3	**B2**	YES

If **Part 2** and **Part 3** met from option 1, **Part 1** needs ONLY the following:

Part 1	**1**	**A1**	YES

Headache day of at least moderate severity: 1 of the following 3 options		
OPTION 1		
1	**A1**	YES
2	**A2**	YES
3	**A3**	Moderate or Severe
OPTION 2		
1	**A1**	YES
2	**C1**	YES
3	**C2**	ERGOT OR TRIPTAN
OPTION 3		
1	**A1**	YES
2	**C2**	Medication Provided
3	**C3**	YES

APPENDIX C. PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Date _____ Patient Name _____ Date of Birth_____

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

Explanation:

1 = No change (or condition has got worse)

2 = Almost the same, hardly any change at all

3 = A little better, but no noticeable change

4 = Somewhat better, but the change has not made any real difference

5 = Moderately better, and a slight but noticeable change

6 = Better, and a definite improvement that has made a real and worthwhile difference

7 = A great deal better, and a considerable improvement that has made all the difference

Patient's signature: X _____

Do not write in this box - FOR OFFICE USE ONLY.

NOTE TO HEALTH CARE PROVIDER

A significant, favorable change is a score of 5- 7

No significant change is a 1-4 response.

Note, this is a dichotomous scale (5-7 = yes; 1-4 = no).

A 2-point change is significant from their last reported score.

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. Journal of Manipulative Physiological Therapeutics (IMPT) 2004;27:26-35.

APPENDIX D. EXAMPLE SAS CODE

The following sample SAS code pertains to the primary efficacy ANCOVA analysis:

```
ODS OUTPUT DIFFS = XXX LSMEANS = XXX
PROC MIXED DATA = XXX;
        CLASS TREATMENT MIGRAINETYPE PREVENTIVEMEDICATION;
        MODEL CHG = TREATMENT MIGRAINETYPE PREVENTIVEMEDICATION
BASE;
        LSMEANS TREATMENT / CL PDIFF;
RUN;
```

The following SAS code pertains to the main MMRM analysis:

```
ODS OUTPUT DIFFS = XXX LSMEANS = XXX
PROC MIXED DATA=XXX;
        CLASS USUBJID MONTH TREATMENT MIGRAINETYPE
PREVENTIVEMEDICATION;
        MODEL CHG=BASE MONTH TREATMENT MIGRAINETYPE
PREVENTIVEMEDICATION TREATMENT*MONTH;
        REPEATED MONTH/SUBJECT=USUBJID TYPE=UN;
        LSMEANS TREATMENT TREATMENT*MONTH/PDIFF CL ALPHA=0.05;
RUN;
```

The following SAS code pertains to the sensitivity MMRM analysis:

```
ODS OUTPUT DIFFS = XXX LSMEANS = XXX
PROC MIXED DATA=XXX;
        CLASS USUBJID MONTH TREATMENT MIGRAINETYPE
PREVENTIVEMEDICATION;
        MODEL CHG=BASE MONTH TREATMENT MIGRAINETYPE
PREVENTIVEMEDICATION TREATMENT*MONTH BASE*MONTH;
        REPEATED MONTH/SUBJECT=USUBJID TYPE=UN;
        LSMEANS TREATMENT TREATMENT*MONTH/PDIFF CL ALPHA=0.05;
RUN;
```

The following SAS code pertains to the MI analysis:

```
PROC MI DATA=XX SEED=98765 OUT=MI_OUT NIMPUTE=100 MAXIMUM=. . . 28 28
28 28  MINIMUM=. . . 0 0 0 0;
            CLASS TRTMI MIGRAINETYPE PREVENTIVEMEDICATION;
            FCS REG(V0=TRTMI MIGRAINETYPE PREVENTIVEMEDICATION
     /DETAILS) NBITER=100;
            FCS REG(V1=TRTMI MIGRAINETYPE PREVENTIVEMEDICATION
     V0 /DETAILS) NBITER=100;
            FCS REG(V2=TRTMI MIGRAINETYPE PREVENTIVEMEDICATION
     V0 V1/DETAILS) NBITER=100;

            FCS REG(V3=TRTMI MIGRAINETYPE PREVENTIVEMEDICATION

            V0 V1 V2/DETAILS) NBITER=100;
            VAR TRTMI MIGRAINETYPE PREVENTIVEMEDICATION V0 V1 V2 V3;
RUN;
```

where TRTMI is the placebo reassigned treatment group.

The output dataset from the below SAS code will contain the estimate of the mean difference and the standard error of the estimate from each of the 100 datasets

```
ODS OUTPUT DIFFS=DIFF LSMEANS=LSM;
PROC MIXED DATA=UPDATED_MI_OUT METHOD=REML;
     BY   IMPUTATION;
     CLASS TREAT MIGRAINETYPE PREVENTIVEMEDICATION;
     MODEL CHG=BASE TREAT MIGRAINETYPE PREVENTIVEMEDICATION;
     LSMEANS TREAT/DIFF;
RUN;
```

where TREAT is the planned randomized treatment group.

SAS PROC MIANALYZE code is as follows;

```
ODS OUTPUT PARAMETERESTIMATES=PARMEST;
PROC MIANALYZE DATA=MIXED_OUT ALPHA=0.05 THETA0=0;
     BY TREAT;
     MODELEFFECTS ESTIMATE;
     STDERR STDERR;

RUN;
```

where TREAT is the planned randomized treatment group.

The following SAS code pertains to the logistic regression analysis:

```
PROC LOGISTIC DATA = XXX;
        CLASS TREATMENT (REF = '1') MIGRAINETYPE
    PREVENTIVEMEDICATIONUSE / PARAM = REF;
        MODEL RESPONSE (EVENT = '1') = TREATMENT MIGRAINETYPE
    PREVENTIVEMEDICATIONUSE BASELINE;
RUN;
```