# Statistical Analysis Plan

A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-Label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

Study Number TV48125-CNS-20024

NCT03347188

SAP Approval Date: 06 April 2020

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**Phase 2**

**IND number: 106533; EudraCT number: Not Applicable**

**Approval Date: 06 April 2020**

**Sponsor**

**Teva Branded Pharmaceutical Products R&D, Inc.**
**145 Brandywine Parkway**
**West Chester, Pennsylvania 19380**
**United States of America**

**Prepared by:** [redacted]

# STATISTICAL ANALYSIS PLAN APPROVAL

**Study No.:** **TV48125-CNS-20024**

**Study Title:** A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-Label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

**Statistical Analysis Plan for:**

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

**Amendment: 0**

**Author:** [redacted]

[redacted] 4/2/2020

**Approver:** [redacted] **Date**

[redacted]

[redacted] 06 APR 2020

**Approver:** [redacted] **Date**

[redacted]

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| ADA | antidrug antibodies |
| ANCOVA | analysis of covariance |
| β-HCG | beta-human chorionic gonadotropin |
| CMH | Cochran-Mantel-Haenszel |
| CNS | central nervous system |
| CRF | case report form |
| CV | coefficient of variation |
| e-diary | electronic diary |
| ECG | electrocardiogram/electrocardiography |
| eC-SSRS | electronic Columbia Suicide Severity Rating Scale |
| EOS | end of study |
| EOT | end of treatment |
| EODBT | end of double-blind treatment |
| ET | early termination |
| DB | Double-blind |
| FAS | full analysis set |
| GCS | Glasgow coma scale |
| HIT-6 | 6-item Headache Impact Test |
| IMP | investigational medicinal product |
| IRT | interactive response technology |
| ITT | intent-to-treat |
| LS | least square |
| MCS | Mental Health Composite Scores |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAID | non-steroidal anti-inflammatory drug |
| OL-ITT | Open-label intent-to-treat |
| PCS | Physical Composite Scores |
| PDAESI | protocol-defined adverse events of special interest |
| PGIC | Global Impression of Change |
| PP | per-protocol |
| PTH | posttraumatic headache |

| Abbreviation | Term |
|---|---|
| R&D | Research and Development |
| MMRM | mixed model for repeated measures |
| SAC | Standardized Assessment of Concussion |
| SAP | statistical analysis plan |
| sc | subcutaneous(ly) |
| SCAT-3 | Sport Concussion Assessment Tool 3rd edition |
| SD | standard deviation |
| SE | standard error |
| SF-12 | 12-Item Short-Form Health Survey |
| SI | standard international |
| SOC | system organ class |
| SOP | standard operating procedure |
| ULN | upper limit of normal |
| UN | unstructured covariance |
| WHO Drug | World Health Organization Drug Dictionary |

# INTRODUCTION

This Statistical Analysis Plan describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. study TV48125-CNS-20024, [a phase 2, multicenter, randomized, proof-of-concept, double-blind, placebo-controlled, parallel-group study, including an open-label period, evaluating the efficacy and safety of 1 subcutaneous dose regimen of fremanezumab for the treatment of posttraumatic headache (PTH)], 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 regard 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.

# 1. STUDY ENDPOINTS

## 1.1. Primary Efficacy Endpoints

The **primary efficacy endpoint** is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.

## 1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- proportion of patients reaching at least 50% reduction from baseline (*baseline* period) in the monthly average number of headache days of at least moderate severity during the *12-week* period of treatment with the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP
- mean change from baseline (*baseline* period) in the number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- mean change from baseline (*baseline* period) in the number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP
- mean change from baseline (*baseline* period) in the number of headache days of at least moderate severity during the 9- to *12-week* period after the first dose of the IMP
- mean change from baseline (visit 2) in disability score, as measured by the 6-item Headache Impact Test (HIT-6) at week 12 after the first dose of the IMP
- mean change from baseline (visit 2) in the assessment of patient satisfaction, as measured by the Patient Global Impression of Change scale, at 4, 8, and 12 weeks after the first dose of the IMP

## 1.3. Safety Endpoints

The safety and tolerability endpoints are as follows:

- occurrence of adverse events during the study
- clinically significant changes in physical examinations, including body weight

- clinical laboratory (serum chemistry, hematology and coagulation, and urinalysis) test results at each visit
- vital signs (blood pressure, respiratory rate, body temperature, and pulse) 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 each visit
- use of concomitant medication during the study
- number (%) of patients who did not complete the study (day 168, end of study)
- number (%) of patients who did not complete the study due to adverse events
- local tolerability at the injection site (ie, erythema, induration, ecchymosis, and pain) at the following time points postdose: day 0, day 28, and day 56
- hypersensitivity reaction assessment
- Columbia Suicide Severity Rating Scale (C-SSRS)

## 1.4. Immunogenicity Assessment Endpoints

The immunogenicity endpoints are antidrug antibodies (ADA) incidence and characteristics (eg, titer, kinetics, and neutralizing activities).

## 1.5. [redacted]

- [redacted]

- [redacted]

## 1.6. Estimand for Primary Efficacy Endpoint

The primary estimand for this study is defined by the following 4 components:

1. **Target population**: male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by International Classification of Headache Disorders 3rd revision [ICHD-3] (beta version) criteria).
2. **Outcome measure**: mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12 week period after the first dose of the IMP.
3. **Analysis set and handling of intercurrent events**: The full analysis set (FAS) will be used for efficacy analyses. FAS is a subset of the ITT analysis set including only patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy assessment on the primary endpoint. In the FAS, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

For patients randomized to active treatment who did not complete the double-blind treatment period due to lack of efficacy, death, or adverse event, the average number of headache days in the remainder of the analysis window will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to placebo.

All other missing data for patients in either treatment group will be handled as follows:

- For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number of headache days will be calculated based on data available in that analysis window and prorated to 28 days
- For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed using the mean monthly average of

headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data.

More details are provided in Section 6.1.4.

4. **Measure of treatment effect**: analysis of covariance model including treatment as fixed effect and the baseline number of headache days of at least moderate severity and the posttraumatic headache onset (<12 months and ≥12 months) as covariates.

# 2. STUDY DESIGN

## 2.1. General Design

This is a multicenter, randomized, proof-of-concept, double-blind, placebo-controlled, parallel-group study, including an open-label period, evaluating the efficacy and safety of 1 subcutaneous (sc) dose regimen of fremanezumab in adult patients with PTH. The study will consist of a screening visit, a baseline period, a double-blind treatment period lasting approximately 12 weeks, and an open-label period lasting approximately 12 weeks.

The total duration of patient participation in the study is planned to be approximately 28 weeks.

Patients will complete a screening visit (visit 1) after providing informed consent, and eligible patients will enter a baseline period lasting approximately 4 weeks (28+3 days), during which time they will enter their baseline PTH information into a daily electronic headache diary (e-diary). Patients meeting eligibility requirements will be randomly assigned to 1 of 2 treatment groups with fremanezumab or placebo in a 1:1 ratio. Treatment assignment will take place with stratification based on the duration of the patient's history of PTH (<12 months and ≥12 months duration).

Screening results will be reviewed for eligibility, additional baseline assessments will be administered, and the first treatment administration will occur at visit 2. Patients will return to the study center approximately every 4 weeks (visit 3 and visit 4) for a continuation of the blinded treatment administered subcutaneously (sc); for safety and efficacy assessments; and for blood and urine sampling for pharmacokinetics, immunogenicity, and biomarker analysis. At visit 5, all patients will proceed directly to an open-label treatment phase, with fremanezumab administered sc. Patients will then return to the study center approximately every 4 weeks (visits 6 and 7) for continued open-label treatment and safety tolerability and efficacy assessments. Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP.

A database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.

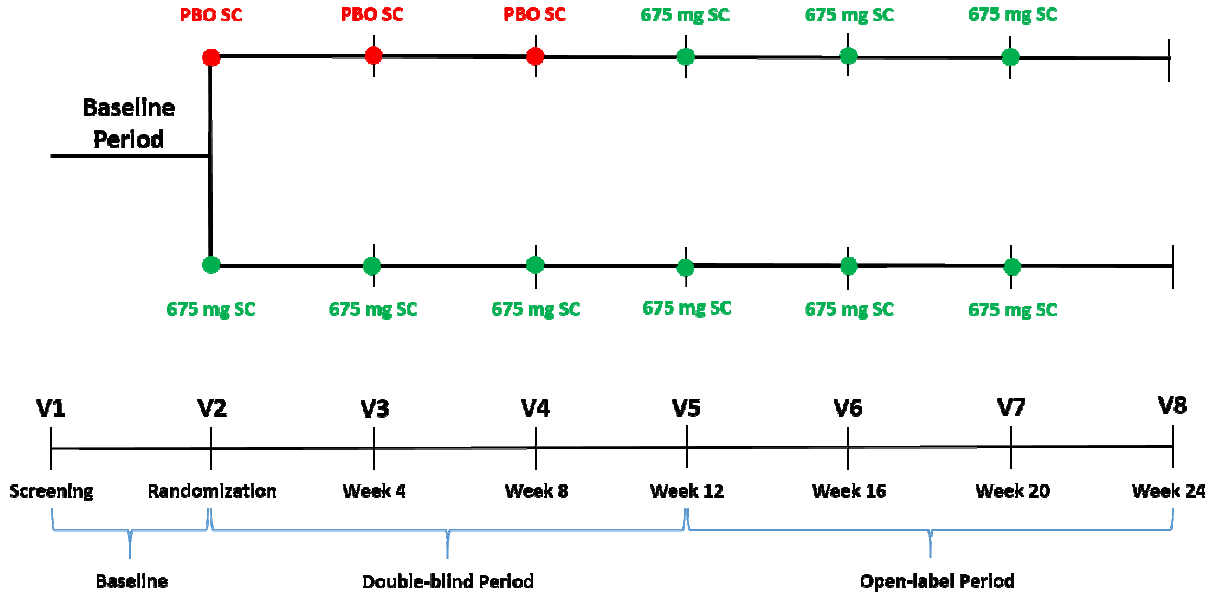
Patients who complete all scheduled visits will have procedures and assessments performed at visit 8. Patients who withdraw from the study before completing either the double-blind or the open-label treatment phases will have visit 8 procedures and assessments performed at their final visit. For all patients in the study, the end-of-treatment visit (visit 8) is defined as the final visit of the study and the conclusion of all study activities for the patient; patients will not receive any further treatments with IMP and will be treated according to guidelines and treating physicians' discretion.

In the open-label period patients will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20).

The end of study is defined as the last safety visit. However, a final database lock will occur following the end-of-treatment visit (visit 8) of the last patient for analysis of the study data.

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

**Figure 1: Overall Study Schematic Diagram**




PBO=placebo; SC=subcutaneous; V=visit.

## 2.2. Randomization and Blinding

Patients meeting eligibility requirements will be randomized into one of the following treatment groups:

1. **Arm A**: Fremanezumab 675-mg sc treatment group

   Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).

2. **Arm B**: Placebo treatment group

   Patients randomized to placebo will receive placebo administered as 3 sc injections (1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).

The randomization code will be generated by the interactive response technology (IRT) third-party vendor according to specifications from the Biostatistics Department. A Teva statistician will be responsible for reviewing the dummy randomization codes, and the final randomization code will be maintained by the third-party vendor in a secure location.

After all patients have completed visit 5 and an unblinding request from the Teva statistician has been received, the third-party vendor will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure (SOP).

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment during the double-blind treatment period of the study.

## 2.3. Data Monitoring Committee

Not applicable.

[redacted]

## 2.5. Sequence of Planned Analyses

### 2.5.1. Planned Interim Analyses

There will be no interim analysis. However, a database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind treatment period.

### 2.5.2. Final Analyses and Reporting

A database lock from the double-blind treatment period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind treatment period. This SAP will be finalized before the database lock.

All endpoints related to the double-blind treatment period will be analyzed, including data up to visit 5.

Data collected from open-label treatment period (visit 5 and after) will be analyzed separately after study completion.

# 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. Open-Label Intend-to-Treat Analysis Set

The open-label ITT (OL-ITT) analysis set is a subset of the ITT analysis set including only patients who receive at least 1 dose of study drug during the open-label treatment period.

Note, OL-ITT will be used for open-label analysis.

## 3.3. Safety Analysis Set

The safety analysis set will include all randomized patients who receive at least 1 dose of the IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received in the double-blind treatment period, regardless of the treatment to which they were randomized, unless otherwise specified.

Patients randomized to placebo group but received any number of injection of fremanezumab in error will be analyzed in a separated group (Other) in the safety analyses if applicable.

## 3.4. Full Analysis Set

The full analysis set (FAS) is a subset of the ITT analysis set including only patients who receive at least 1 dose of the IMP and have at least 1 post-baseline efficacy assessment on the primary endpoint.

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

## 3.5. Per-Protocol Analysis Set

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any major protocol deviations. Major protocol deviations will be determined before unblinding and database lock.

## 3.6. Patients in Extension or Open-Label Period

This will include patients continued in the extension or open-label period.

# 4. GENERAL ISSUES FOR DATA ANALYSIS

## 4.1. General

Descriptive statistics for continuous variables include count (n), mean, SD, standard error (SE), median, minimum, and maximum. In addition, for fremanezumab concentration, percentage coefficient of variation (%CV) and geometric mean will also be calculated. Descriptive statistics for categorical variables include patient counts and percentages, and a missing category will be displayed as appropriate.

Summaries of potentially clinically significant abnormal values for clinical laboratory tests and vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits).

## 4.2. Specification of Baseline Values

For analyses of the double-blinded treatment period, baseline is the last observed data before the administration of the first dose of the IMP, unless otherwise noted. For data collected in the e-diary daily, baseline will be derived from the baseline period (from the day of the informed consent to before the administration of the first dose of the IMP) and prorated to 28 days if the number of days in the baseline period is not equal to 28. Details are provided in Section 6.1.

For analyses of the open label treatment period, the baseline is the observed data at visit 5, unless otherwise noted.

## 4.3. Handling Withdrawals and Missing Data

For efficacy analyses based on e-diary data, the missing data handling methods are provided in Section 6.1.4. For the efficacy analyses based on non-e-diary data, missing data handling methods, if applicable, will be provided in the efficacy analysis section for that endpoint.

Dates that have incomplete information (ie. only month and year or only year recorded) will be estimated for the purpose of calculating variables that are dependent on time if necessary. Day will be estimated as the first day (01) of the month (if month and year of partial date are available) or middle (July 1) of the year (if only year is available), unless otherwise noted. If no date information is recorded, the date will not be imputed.

The imputations for partial dates are only for calculation purpose. Original date variables will not be modified. Listings will present dates as collected. If no date information is recorded, the date will not be imputed.

## 4.4. Study Days and Visits

For 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 scheduled and unscheduled assessments), except for triplicate ECG assessments (see Section 8.11 for further details).

Study visits are detailed in Table 1.

**Table 1: Study Visits**

| Visit # | V1 (Screening) | Double-Blinded Treatment Period | | | Open-Label Period | | | |
|---|---|---|---|---|---|---|---|---|
| | | V2[1] | V3 | V4 | V5[2] | V6 | V7 | V8 |
| **Day** | **-28 to-1** | 0±3 | 28±3 | 56±3 | 84±3 | 112±3 | 140±3 | 168±3 |
| **Week** | **-** | 0 | 4 | 8 | 12 | 16 | 20 | 24 |
| | **Visit 1** | Visit 2 Dose 1 | Visit 3/ Dose 2 | Visit 4/ Dose 3 | Visit 5/ Dose 4/ **EODBT** | Visit 6/ Dose 5 | Visit 7/ Dose 6 | Visit 8/ EOT/EOS/ET[3] |

[1] Baseline/Randomization
[2] Visit 5 is the end of double-blind treatment period and the beginning of open-label period
[3] EOT=the end of treatment; EOS=end of study; ET=early termination

The end of double-blind treatment period (EODBT) is defined as Visit 5/Week 12 or early termination (ET) visit for patients did not complete double-blind treatment period and did not continue in open-label period.

'Last Assessment' may be derived for analysis purpose for safety data and is defined as the last observed postbaseline data during the double-blind treatment period for double-blind period or the last observed postbaseline data during the open-label treatment period for open-label period.

For patients who withdraw from the study early, their data at the early withdrawal visit will be excluded from the by-visit summaries but will be included in the 'Last Assessment' summaries.

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

For data from the e-diary, monthly analysis windows [Month 1 (weeks 1 to 4), Month 2 (weeks 5 to 8), and Month 3 (weeks 9 to 12)] will be derived for the purpose of efficacy endpoint analyses. Details are provided in Section 6.1.3.

# 5. STUDY POPULATION

## 5.1. General

The ITT analysis set (see Section 3.1) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and all patients.

## 5.2. Patient Disposition

Data from patients screened; patients screened but not randomized and reason not randomized; patients randomized (ITT); patients randomized but not treated; patients in the safety and other analysis sets; patients who completed the double-blind treatment; patients who enter open-label treatment period; patients who did not compete double-blind treatment will be summarized using descriptive statistics. Data from patients who did not complete double-blind treatment will also be summarized by reason using descriptive statistics.

This summary will include all patients.

Patients who completed study or patients withdrew from the study by reason will be summarized once the study is completed.

## 5.3. Demographics and Baseline Characteristics

The demographic data will be collected at the screening visit after the patient signs the informed consent form. Patient demographic data including age, age group (<65 or ≥65 years old), gender, race, race group (white or other), ethnicity, baseline weight (kg), baseline height (cm), and baseline body mass index ($kg/m^2$) will be summarized using descriptive statistics for all analysis sets.

Baseline characteristics including time since the head trauma, duration of PTH history (less than 12 month since the brain injury versus greater or equal to 12 month since the brain injury), diagnosis of PTH, preventive medication use (yes or no) at screening or baseline, use of any acute headache medication (opioid, barbiturate, triptan, and NSAIDS) during the baseline period (yes or no), use of prescription abortive headache medication (opioid, barbiturate, and triptan) during the baseline period (yes or no), and monthly average number of headache days of at least moderate severity during the baseline period will be summarized for the ITT analysis set using descriptive statistics. No inferential analyses will be performed.

The time (in year) since the head trauma will be calculated as (the date of informed consent – the date of head trauma + 1)/365.25. Rules for handling partial head trauma date are in Section 4.3.

## 5.4. Medical History

All medical history abnormalities will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each SOC and only once in each preferred term.

## 5.5. Prior Therapy and Medication

All prior medications or therapy will be coded using the World Health Organization Drug Dictionary of medical codes (WHO Drug). The incidence of prior medications or therapy will be summarized by therapeutic class and preferred term using descriptive statistics. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken within 3 months prior to the administration of the first dose of the IMP.

The prior medications will be summarized by the following indications categories:

- butalbital for post traumatic headache
- butalbital for other reason than post traumatic headache
- ergots for post traumatic headache
- ergots for other reason than post traumatic headache
- NSAIDS for post traumatic headache
- NSAIDS for other reason than post traumatic headache
- opioids for post traumatic headache
- opioids for other reason than post traumatic headache
- preventive medication from the study protocol for post traumatic headache
- preventive medication from the study protocol for other reason than post traumatic headache
- triptans for post traumatic headache
- triptans for other reason than post traumatic headache
- other

## 5.6. Childbearing Potential and Methods of Contraception

Information related to reproductive system findings will be collected at the screening visit. Data will be listed.

## 5.7. Physical Examinations

Patients with at least 1 abnormal finding (overall) and abnormal findings for each category will be summarized.

## 5.8. Study Protocol Deviations

Data from patients with any important protocol deviations during the study will be summarized overall and for each category using descriptive statistics.

# 6. EFFICACY ANALYSIS

## 6.1. General

The FAS will be used for all efficacy analyses unless otherwise noted. Analyses of the primary and secondary endpoints will be repeated for the PP analysis set.

Analyses for endpoints related to double-blind treatment (up to visit 5/12-week) will be performed after DB lock for double-blind treatment. The analyses will be by treatment groups.

Analyses for endpoints related to open-label treatment (from visit 5/12-week to the end of the study) will be performed after study completion.

For data not collected daily, baseline is the last observed data before the administration of the first dose of the IMP. For data collected daily in the e-diary, baseline will be derived from the baseline period (from the day of the informed consent to before the administration of the first dose of the IMP). Details are provided in Section 6.1.3.

For patients who do not have Visit5/Week 12 assessment and do not continue in the open-label period but have assessment at EOS, the assessment at EOS will be used as Visit 5/Week 12.

Derived efficacy variables are

- monthly average number of headache days of at least moderate severity
- monthly average number of headache days of any severity
- monthly average number of neck pain days of any severity
- monthly average number of days of use of any acute headache medication
- monthly average number of days of use of opioid analgesics for headache
- average severity of headache
- average daily peak headache severity

Summaries will be presented by treatment group as randomized unless otherwise noted. In addition to inferential statistics, descriptive statistics will be presented in by-visit or by-analysis-window summaries. A missing category will be presented if applicable. Derived endpoints will be listed.

### 6.1.1. Posttraumatic Headache Data from E-diary

Information about PTH will be recorded in the e-diary daily. Corresponding PTH questions are in Appendix A (questions A1, B1 through B3, and C1 through C9). Patients will record headache(s) occurred during last 24 hours. The recording window on e-diary device is "Yesterday morning 6:00 am to today at 5:59 am". Patients can record missed entry for "the day before yesterday morning 6:00 am to yesterday at 5:59 am", maximum 48 hours recall window is allowed.

Date of a headache is derived as the following

- headache report date -1 day if the recording is for 24 hours recall
- headache report date – 2 days if the recording is for 48 hours recall

Baseline and postbaseline monthly average number of headache days for a patient within an analysis window will be calculated based on data available and prorated to 28 days using formula A.

### 6.1.2. Data Derivation

The **monthly average** of an efficacy variable will be calculated and prorated to 28 days as follows:

$$\frac{\sum efficacy\ endpoint\ data\ during\ the\ period}{Number\ of\ Days\ with\ assessments\ recorded\ in\ the\ eDiary\ during\ the\ period} \times 28 \quad [A]$$

The "efficacy endpoint data" will be "number of headache days of at least moderate severity", "number of headache days of any severity", "number of neck pain days of any severity", "number of days of use of any acute headache medication", and "number of days associated with use of opioid analgesics for headache" observed during a treatment period.

The "period" will be the baseline period for baseline calculation or 12-week double-blind treatment period or monthly analysis window [eg. Month 1 (weeks 1 to 4), Month 2 (weeks 5 to 8), Month 3 (weeks 9 to 12)] for post-baseline calculations.

The **percentage of reduction** from baseline in the monthly average number of headache days will be calculated as follows:

$$\frac{baseline\ value - postbaseline\ value}{baseline\ value} \times 100\% \quad [B]$$

where baseline value and postbaseline value are the monthly average calculated using formula A.

### 6.1.3. Analysis Windows for E-diary Data

**Baseline** window is the period from the day of the informed consent to before the administration of the first dose of the IMP. The baseline monthly average value for an efficacy variable will be calculated based on data recorded in the baseline window and prorated to 28 days using formula A.

**Postbaseline 4-week (monthly) analysis windows** will be determined based on the actual dosing date as follows:

- Month 1 (weeks 1 to 4): from the day of the first dose of the IMP administration to the day before the IMP administration at visit 3 (week 4/dose 2) or to the end of e-diary in the double-blind treatment period if a patient only receives dose 1;
- Month 2 (weeks 5 to 8): from the day of the IMP administration at visit 3 (week 4/dose 2) to the day before the IMP administration at visit 4 (week 8/dose 3) or to the end of e-diary in the double-blind treatment period if a patient only receives dose 1 and dose 2;

- Month 3 (weeks 9 to 12): from the day of the IMP administration at visit 4 (week 8/ dose 3) to the end of e-diary of the double-blind treatment period.

Notes:

1. The end of e-diary of the double-blind treatment period is defined as the date of last IMP administration + 27 days.
2. There will be no double-blind IMP administration at visit 5;
3. A 4-week analysis window may contain <28, 28, or >28 days.

The monthly average of an efficacy variable for each analysis window will be calculated based on data recorded in the e-diary and prorated to 28 days using formula A. Missing data handling methods are provided in Section 6.1.4.

### 6.1.4. Handling Missing E-diary Data

This section includes missing data handling for e-diary data. For other type of data, the missing data handling methods are provided in the analysis section for the endpoint if applicable.

**For analyses using ANCOVA or mixed model for repeated measures (MMRM**) based on monthly averages the missing data handling methods are as follows:

For patients randomized to active treatment group and did not completed the double-blind treatment period due to lack of efficacy, death, or adverse event, the number of headaches in an analysis window will be imputed as the following

$$\sum (\text{observed headaches during a analysis window}) + (N\text{-}X)*(\textit{placebo average}/N)$$

Where
$N$ denotes the number of days in the analysis window, 84 days for 12-week analysis window and 28 days for 4-week analysis window;
$X$ ($X$>0) denotes the number of days with e-diary within the analysis window;
"*Placebo average*" is the monthly average of number of headache during the analysis window from placebo patients who completed study.

For 12-week analysis window, the monthly average of the number of headaches will be prorated to 28 days using formula A;

All other missing data for patients in either treatment group will be handled as follows:

- For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number of headache days will be calculated based on data available in that analysis window and prorated to 28 days using formula A;
- For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed using the mean monthly average of headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data.

**Note: the imputation is only for post-baseline data and applies to all efficacy endpoints related to the number of headache days.**

In addition, as a sensitivity analysis, the primary endpoint will be analyzed using a MMRM method. Detail is provided in Section 6.2.3.

## 6.2. Primary Efficacy Endpoint and Analysis

### 6.2.1. Definition

The primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.

The primary efficacy endpoint for this study will be derived from PTH data (presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.

Headache days of at least moderate severity will be derived from the e-diary data as described in Section 6.1.1. The 12-week period is the period from administration of the first dose of IMP to the EODBT as defined in Section 4.4. The monthly average number of headache days of at least moderate severity will be calculated using formula A. Missing data handling method is provided in Section 6.1.4.

### 6.2.2. Primary Efficacy Analysis

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 $\delta_1$ and $\delta_2$ are the estimates of mean change from baseline in the monthly average number of headache days of at least moderate severity for the fremanezumab treatment group and the placebo group, respectively.

The primary endpoint will be analyzed using an ANCOVA method. The model will include treatment as fixed effect and the baseline monthly average number of headache days of at least moderate severity and the posttraumatic headache onset (<12 months and ≥12 months) as covariates. The least square (LS) mean and SE for each treatment group, LS means and corresponding 95% confidence intervals for the treatment differences (fremanezumab - placebo), and associated p-values will be presented.

The analysis will be performed on the FAS and PP analysis sets.

Example SAS code for ANCOVA

**PROC MIXED DATA**=<name>;

**CLASS** TRTP ONSET;

**MODEL** CHG= BASE ONSET TRTP /**S**;

**LSMEANS** TRTP /**DIFF=CONTROL** (“Placebo”) **CL ALPHA**=0.05;

**ODS OUTPUT LSMEANS**= <name> **DIFFS**= < name> ;

**RUN;**

Where TRTP denotes the planned treatment group; CHG denotes the change from baseline in the monthly average number of headache days of at least moderate severity; BASE denotes the baseline monthly average number of headache days of at least moderate severity; ONSET denotes the posttraumatic headache onset (<12 months and ≥12 months). In bold are the SAS key words.

### 6.2.3. Sensitivity Analysis for the Primary Efficacy Endpoint

A sensitivity analysis will be conducted to explore the impact of missing data in the primary efficacy analysis.

MMRM analysis will be utilized to estimate the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP.

Postbaseline data will include data from 3 monthly analysis windows (Month 1, Month 2, and Month 3) derived using the algorithm described in Section 6.1.3.

The MMRM will include the posttraumatic headache onset (<12 months and ≥12 months), treatment, month (3 levels), and month-by-treatment interaction as fixed effects and baseline monthly average number of headache days of at least moderate severity as a covariate. The unstructured covariance structure (UN) will be used to model intra-subject correlation. LS mean and SE for each treatment group, LS means and corresponding 95% confidence intervals for the treatment differences (fremanezumab - placebo), and the associated p-values from the overall results for treatment comparisons on the average of months 1 to 3 will be presented to support the primary analysis. Notes: if UN dose not converge, the hierarchy uses the first-order autoregressive structure [AR-(1)] and the compound-symmetry structure (CS).

Example SAS codes for MMRM analysis:

**PROC MIXED DATA**=<name> **METHOD**=**REML**;

**CLASS** USUBJID TRTP ONSET AVISIT;

**MODEL** CHG=BASE ONSET TRTP AVISIT TRTP*AVISIT/**S;**

**REPEATED** AVISIT/ **SUB**=USUBJID **TYPE=UN**;

**LSMEANS** TRTP TRTP*AVISIT/ **DIFF CL ALPHA=0.05**;

**ODS OUTPUT LSMEANS**= <name> **DIFFS**= < name> ;

**RUN;**

Where TRTP denotes the planned treatment group; ONSET denotes the posttraumatic headache onset (<12 months and ≥12 months); AVISIT denotes the analysis window; BASE denotes the baseline monthly average number of headache days of at least moderate severity; CHG denotes the change from baseline.

The analysis will be performed on the FAS.

## 6.3. Secondary Efficacy Endpoints and Analyses

The key secondary efficacy endpoints are listed in Section 1.2. Analyses will be based on the FAS and PP analysis sets.

### 6.3.1. Proportion of Patients Reaching at Least 50% Reduction From Baseline in the Monthly Average Number of Headache Days of at Least Moderate Severity During 12-Week Period of Treatment with the IMP

This secondary efficacy endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by the posttraumatic headache onset (<12 months and ≥12 months). Descriptive statistics (count and percent) and p-value for Row Mean Scores difference will be presented.

The 12-week period is the period from the first dose of the IMP to the EODBT as defined in Section 4.4. Headache during the 12-week period will be derived from the e-diary data as described in Section 6.1.1. The monthly average number of headache days of at least moderate severity will be calculated using formula A. Missing data handling methods are provided in Section 6.1.4 .

The proportion of reduction for a patient will be calculated using formula B. Responders will be those with ≥50% reduction.

Example SAS code for CMH:

**PROC FREQ DATA**=<name>;

**TABLES** ONSET*TRTP*AVALC / **CMH**;

**OUTPUT OUT**=<name> **CMH**;

**RUN**;

Where TRTP denotes the planned treatment group; ONSET denotes posttraumatic headache onset (<12 months and ≥12 months); and AVALC denotes the responses with yes for responders (with ≥50% reduction) and no for non-responders (with <50% reduction).

### 6.3.2. Proportion of Patients Reaching at Least 50% Reduction From Baseline in the Monthly Average Number of Headache Days of at Least Moderate Severity During First 4-Week, 5- to 8-Week, and 9- to 12-Week Periods of Treatment with the IMP

The following endpoints will be analyzed using CMH test in a manner analogous to the analysis described in Section 6.3.1, respectively.

- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP

- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP

Postbaseline data will include data from 3 monthly analysis windows (Month 1/1- to 4-Week, Month 2/5- to 8-week, and Month 3/9- to 12 week) derived using the algorithm described in Section 6.1.3. Data in each analysis window will be prorated to 28 days using formula A. Headache of at least moderate severity within each analysis window will be derived from the e-diary data as described in Section 6.1.1. The proportion of reduction for a patient will be calculated using formula B for each analysis window. Responders will be those with ≥50% reduction.

### 6.3.3. Mean Change from Baseline in the Number of Headache Days of at Least Moderate Severity During the First 4-Week, 5- to 8-Week, and 9- to 12-Week Periods after the First Dose of the IMP

The following endpoints will be analyzed using MMRM method in a manner analogous to the analysis described in Section **6.2.3.**

- mean change from baseline *(*baseline period) in the number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP
- mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP

Postbaseline data will include data from 3 monthly analysis windows (Month 1/1- to 4-Week, Month 2/5- to 8-week, and Month 3/9- to 12 week) derived using the algorithm described in Section 6.1.3. Data in each analysis window will be prorated to 28 days using formula A. Headache of at least moderate severity within each analysis window will be derived from the e-diary data as described in Section 6.1.1.

Results for each endpoint will be separated from PROC MIXED outputs. The results from the last analysis window will be presented.

### 6.3.4. Mean Change From Baseline in Disability Score, as Measured by the 6-Item Headache Impact Test (HIT-6) at Week 12 After the First Dose of the IMP

The HIT-6 (Appendix B) is a tool used to measure the impact headaches have on a patient's normal daily life and ability to function. The HIT-6 consists of 6 items, including pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Each item is answered on a 5-point Likert scale (6 = never, 8 = rarely, 10 = sometimes, 11 = very often, or 13 = always), which are summed to produce a total score that ranges from 36 to 78, with larger scores reflecting greater impact of headache on the daily life of the patient.

During the double-blind treatment period patients will complete the HIT-6 questionnaire at visit 2 and visit 5/week 12 before the administration of the IMP or at ET visit.

The HIT-6 total score mean change from baseline at visit 5/week 12 will be analyzed using an ANCOVA method in a manner analogous to the analysis described in Section 6.2.2.

Categorical and numerical responses for each of 6-item questions will be summarized using descriptive statistics by visit.

#### 6.3.5. Mean Change From Baseline in the Assessment of Patient Satisfaction, as Measured by the Patient Global Impression of Change Scale, at 4, 8, and 12 Weeks after the First Dose of the IMP

The PGIC is a validated generic tool for the assessment of overall change in the severity of illness following treatment.

During the double-blind treatment period patients will complete the HIT-6 questionnaire at visit 2 and visit 5/week 12 before the administration of the IMP or at ET visit.

During the double-blind treatment period, at visit 2/week 0, visit 3/week 4, visit 4/week 8, visit 5/week 12 before the administration of the IMP or at ET visit, patients will rate how they feel compared with how they felt before receiving IMP using the following 7-point scale:

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

For analysis purposes, a dichotomous scale of ‘Yes’ or ‘No’ will be derived. A favorable change is score of 5-7, which means there is significant improvement (Yes) with the treatment. If the response is 1-4, it is considered no significant improvement (No).

The percentage of patients’ dichotomous scale of ‘Yes’ or ‘No’ of PGIC assessments at baseline (week 0/visit 2), weeks 4, 8, and 12 (visits 3 to 5) will be analyzed using a CMH method in a manner analogous to the first secondary endpoint described in Section 6.3.1. Missing data will not be imputed.

Raw data for these visits will be summarized using descriptive statistics. Missing category will be presented if applicable.

## 6.4. [redacted]

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# 7. MULTIPLE COMPARISONS AND MULTIPLICITY

A fixed-sequence (hierarchical) testing procedure will be implemented to control the type 1 error rate at 0.05.

Testing of statistical significance at a 2-sided alpha of 0.05, fremanezumab 675-mg sc treatment group versus placebo group, will be performed for the primary endpoint. If the primary endpoint meets statistical significance, then each of the key secondary endpoints will be tested for significance in a pre-specified order at a 2-sided alpha of 0.05. If and when any p>0.05, no further comparisons will be interpreted inferentially.

The sequence of comparisons will be as follows:

1. **Primary endpoint** (mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP)
2. **1st key secondary endpoint** (proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of any severity during the 12-week period of treatment with the IMP)
3. **2nd key secondary endpoint** (mean change from baseline (visit 2) in disability score, as measured by the 6-item Headache Impact Test (HIT-6) at week 12 after the first dose of the IMP)

# 8. SAFETY ANALYSIS

## 8.1. General

For double-blind treatment period (up to visit 5), the safety analysis set will be used for all safety analyses. Summaries will be presented using descriptive statistics by treatment group as actually received unless otherwise stated and overall.

For open-label treatment period (visits 5 to 8/EOT/EOS/ET), OL-ITT analysis set will be used for safety analyses. Changes from baseline or change from visit 5 will be presented. Summaries will be presented using descriptive statistics overall. **The data will be analyzed after the completion of the study.**

## 8.2. Duration of Exposure to Study Drug

### 8.2.1. Double-Blind Treatment Period

During the double-blind treatment period patients will receive 3 sc injections of fremanezumab or placebo at visit 2, visit 3, and visit 4.

Duration of the double-blind treatment period (days) for a patient is defined as the number of days a patient is in the double-blind treatment period and calculated as the date of visit 5 - the first date of the IMP + 1. For patients who do not complete double-blind treatment period, date of visit 5 will be estimated as the date of last IMP administration in double-blind treatment period + 27. Dosing visit interval (days) is defined as the number of days between dosing visit (dose 1 and dose 2; dose 2 and dose 3) and calculated as date of next dosing - date of current dosing.

Duration of the double-blind treatment period (days), dosing visit interval (days), the number of doses received, and total number of injections received will be summarized using descriptive statistics. Summary will be presented by treatment group.

IMP administration and accountability data will be listed.

### 8.2.2. Open-Label Treatment Period

During the open-label treatment period patients will receive 3 sc injections of fremanezumab at visit 5, visit 6, and visit 7.

Duration of the treatment (days) in the study (both in double-blind and open label) for a patient is defined as the number of days a patient is in the study and calculated as the date of visit 8 - the first date of the IMP + 1. Duration of the treatment (days) in the open-label treatment period for a patient is defined as the number of days a patient is in the open-label treatment period and calculated as the date of visit 8 - the date of the IMP at visit 5 + 1. For patients who are do not complete open-label treatment, date of visit 8 will be estimated as the date of last IMP administration + 27.

Duration of the treatment (days) in the study and in the open-label period will be summarized using descriptive statistics.

IMP administration and accountability data will be listed.

## 8.3. Adverse Events

Adverse events will be recorded from time informed consent is obtained through the end of study participation.

The following are considered protocol-defined adverse events of special interest (PDAESI) to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic-related adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT ≥3× ULN, total bilirubin ≥2× ULN, or international normalized ratio >1.5), Hy's Law events, or events of anaphylaxis and severe hypersensitivity.

All adverse events will be coded using MedDRA. Each patient will be counted only once in each preferred term or SOC category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (defined as related or with missing relationship) (overall, overall by severity, serious AEs, PDAESI), serious adverse events, PDAESI, and adverse events causing withdrawal from the study. 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.

Summaries for injection site adverse events will be presented (overall and by severity).

Listings for deaths, serious adverse events, adverse events leading to treatment withdrawn, adverse events leading to study discontinuation, adverse event requiring concomitant or additional treatment, injection site adverse events, PDAESI, and hypersensitivity and suspected anaphylaxis/hypersensitivity reactions related adverse events will be presented. In addition, listings for MedDRA dictionary terms for adverse event descriptions and adverse event preferred terms by patient number and treatment group will be presented.

Spontaneous abortion or an elective abortion due to developmental anomalies will be reported as a serious adverse event (protocol Section 7.2). These serious adverse events will be listed separately if applicable.

Summaries will include treatment-emergent adverse events which are defined as adverse events occurring at or after the first dose of the IMP. The listing will include all adverse events recorded.

Adverse events for patients who did not meet screening criteria will be listed.

## 8.4. Injection Site Assessments

Injection site assessments will be performed immediately (+10 minute) and 1 hour (±15 minutes) after receiving each dose of the IMP at visits 2, 3, and 4. The injection sites will be assessed for erythema, induration, and ecchymosis. More details are in Section 7.9 of the study protocol.

Injection-site reactions should be recorded as adverse events. Injection-site related adverse events will be summary as indicated in Section 8.3.

## 8.5. Hypersensitivity/Anaphylaxis

Patients will be assessed for suspected anaphylaxis/hypersensitivity reactions during and after administration of the IMP at visits 2, 3, and 4. Data will be summarized using descriptive statistics.

The number of patients with suspected anaphylaxis/hypersensitivity reactions and number of suspected anaphylaxis/hypersensitivity reactions per patient will be summarized using descriptive statistics.

The relative time of suspected event will be calculated as date/time of suspected event - date/time of most current IMP administration and summarized using descriptive statistics. If a patient has more than one suspected anaphylaxis reactions, the earliest time will be used for the calculation.

Data will be listed.

## 8.6. Electronic Columbia Suicide Severity Rating Scale

The eC-SSRS 'Baseline/Screening' version will be completed at visit 1, and the eC-SSRS 'Since Last Visit' version will be completed at all other visits (visits 2, 3, 4, and 5), including unscheduled visits. Any positive findings on the eC-SSRS 'Since Last Visit' version require evaluation by a physician or doctoral-level psychologist.

Data for patients with positive findings (having suicidal ideation or suicidal behavior) will be listed.

## 8.7. Deaths

If any patient dies during the study, all relevant information will be discussed in the patient narrative included in the clinical study report.

## 8.8. Clinical Laboratory Tests

Clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis; see protocol Appendix K for the list) will be performed at all study visits using the central laboratory. 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 on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2 of the protocol.

Laboratory test results will be presented in standard international (SI) units in summaries. Laboratory values and changes from baseline to each visit in the double-blind treatment period and Last Assessment (see Section 4.4) will be summarized using descriptive statistics. Shifts (below [low], within [normal], and above [high] the normal range) from baseline to each visit in the double-blind treatment period and the Last Assessment will be summarized using patient

counts. Baseline is defined as the last observed data before the administration of the first dose of the IMP (also see Section 4.2).

The potentially clinically significant abnormal values will be derived using criteria specified in Table 2 based on all postbaseline values (including scheduled, unscheduled, and withdrawal visits). The overall incidence of potentially clinically significant abnormal values will be summarized for laboratory variables using descriptive statistics by treatment group. Listings for patients who have potentially clinically significant abnormal laboratory data will be presented.

**Table 2: Criteria for Potentially Clinically Significant Laboratory Values**

| Test | | Criterion value |
|---|---|---|
| **Serum chemistry** | | |
| ALT | | ≥3x ULN |
| AST | | ≥3x ULN |
| ALP | | ≥3x ULN |
| GGT | | ≥3x ULN |
| LDH | | ≥3x ULN |
| BUN | | ≥10.71 mmol/L |
| Creatinine | | ≥177 µmol/L |
| Bilirubin (total) | | ≥34.2 µmol/L |
| **Hematology** | | |
| Hematocrit | Men | <0.37 L/L |
| | Women | <0.32 L/L |
| Hemoglobin | Men | ≤115 g/L |
| | Women | ≤95 g/L |
| WBC counts | | ≤3 x $10^9$/L<br>≥20 x $10^9$/L |
| Eosinophils | | ≥10% |
| ANC | | ≤1 x $10^9$/L |
| Platelet counts | | ≤75 x $10^9$/L<br>≥700 x $10^9$/L |
| **Urinalysis** | | |
| 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 |

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma- glutamyl transpeptidase; HGB=hemoglobin; LDH=lactate dehydrogenase; RBC=red blood cell; ULN=upper limit of normal range; WBC=white blood cell

Pregnancy tests will be performed for all women of childbearing potential. Test results will be listed.

Current menstruating status (yes or no) will be collected at all female patients. The data will be listed.

### 8.8.1. 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 Section 7.1.5.1 of the study protocol will be included in serious adverse events reporting.

## 8.9. Physical Examinations

Physical examinations will be performed at visits 1, 2, and 5. Any physical examination finding that is judged by the investigator as a clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in Section 7.1.2 of the study protocol.

Abnormal physical examination findings will be listed.

Weight and height will be summarized and listed with vital signs data.

## 8.10. Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, and body temperature) will be measured visit 1 through visit 5. Weight will be measured at all study visits. 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, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2 of the protocol.

Vital signs (including weight) values and changes from baseline to each visit in the double-blind treatment period and the Last Assessment (see Section 4.4) will be summarized using descriptive statistics. The incidence of potentially clinically significant abnormal values will be summarized for selected vital signs using descriptive statistics. Baseline is defined as the last observed data before the administration of the first dose of the IMP (also see Section 4.2).

Table 3 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column. The potentially clinically significant abnormal vital signs values will include all postbaseline values (including scheduled, unscheduled, and early withdrawal visits) for the summaries.

**Table 3: 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 |
| Temperature | ≥38.3°C | Change of ≥1.1°C |

bpm=beats per minute

Height will be measured at screening visit, and data will be listed in the vital sign listing.

## 8.11. Electrocardiography

Triplicate 12-lead ECGs will be collected at study visits. Any ECG 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, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2 of the protocol.

For ECG variables, the mean of recorded results from last three measurements at a visit will be calculated. The mean results and mean changes from baseline to each visit in the double-blind treatment period and Last Assessment (see Section 4.4) will be summarized using descriptive statistics. Baseline is determined based on the last set of observed data before the administration of the first dose of the IMP.

For ECG findings, the worst value of recorded from last three findings at a visit will be used for analysis. Baseline ECG findings and shifts (normal, abnormal not clinically significant, and abnormal clinically significant) from baseline to each visit in the double-blind treatment period, overall (worst value for a patient), and the Last Assessment (worst value of recorded findings from the last visit) will be summarized using patient counts.

## 8.12. Concomitant Medications or Therapies

Concomitant medications, treatments, or procedures will be recorded throughout the study.

All concomitant medications will be coded using the WHO Drug. The incidence of concomitant medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. The concomitant medications will include all medications taken after administration of the first IMP.

The subset of medications or therapies will be summarized by the indication categories as indicated in Section 5.5.

# 9. TOLERABILITY VARIABLES AND ANALYSIS

Injection site reaction adverse events will be listed and summarized descriptively. See Section 8.3.

# 10. PHARMACOKINETIC ANALYSIS

Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point. The summary will be based on the safety analysis set. At the open-label period, pharmacokinetic plasma concentration results will be tabulated descriptively at each planned sampling time point per treatment group. The plasma concentration will be listed by scheduled visits, time points and treatment.

# 11. PHARMACOGENOMIC ANALYSIS

Pharmacogenomic analysis will be conducted to correlate clinical observations (pharmacokinetic, safety, efficacy, or other effects) with genotypes observed in the study. Pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

# 12. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

The pharmacokinetic/pharmacodynamic relationship analysis if performed will be reported separately.

# 13. BIOMARKER ANALYSIS

[redacted]

# 14. IMMUNOGENICITY ANALYSIS

A summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetic profile, fremanezumab efficacy, and clinical safety will be evaluated.

# 15. PLANNED INTERIM ANALYSIS

There will be no formal interim analysis. However, a database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.

# 16. STATISTICAL SOFTWARE

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

# 17. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

None.

# 18. REFERENCES

Scoring Software (v5.0) Copyright© 2004, 2007, 2009, 2010, 2016 QualityMetric Incorporated 24 Albion Road, Bldg 400. Lincoln, R.I. 02865, U.S.A.

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