Statistical Analysis Plan

A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Episodic Cluster Headache

Study Number TV48125-CNS-30056

NCT02945046

SAP Approval Date: 19 June 2019

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Phase 3

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Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **TV48125-CNS-30056**

Study Title: **A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Episodic Cluster Headache**

Statistical Analysis Plan for:

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

Amendment: **0**

Author: [redacted]

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Approver: [redacted] **Date**

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	antidrug antibodies
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR (1)	the first-order autoregressive structure
β-HCG	beta-human chorionic gonadotropin
CGRP	calcitonin gene-related peptide
CH	cluster headache
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CPRA	cumulative proportion of responder's analysis
CRF	case report form
CS	the compound-symmetry structure
CV	coefficient of variation
e-diary	electronic diary
ECG	electrocardiogram/electrocardiography
ECH	episodic cluster headache
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EOT	end of treatment
EQ-5D	EuroQol-5 Dimension
FAS	full analysis set
HADS	Hospital Anxiety and Depression Scale
IMP	investigational medicinal product
FCS	fully conditional specification
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous(ly)
LS	least square
MCS	Mental Health Composite Scores
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed model for repeated measures
NSAID	non-steroidal anti-inflammatory drug

Abbreviation	Term
PCS	Physical Composite Scores
PGIC	Global Impression of Change
PP	per-protocol
PPSI	Patient-Perceived Satisfactory Improvement
R&D	Research and Development
SAP	statistical analysis plan
sc	subcutaneous(ly)
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
WPAI	Work Productivity and Activity Impairment

INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products R&D, Inc. Study TV48125-CNS-30056, (a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens [intravenous/subcutaneous and subcutaneous] of TEV-48125 [fremanezumab] versus placebo for the prevention of episodic cluster headache), and was written in accordance with SOP GBP_RD_702.

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 of this study is the mean change from baseline (run-in period) in the weekly average number of cluster headache (CH) attacks during the 4-week period after administration of the first dose of the investigational medicinal product (IMP), ie, based on week 0 to 4 data.

1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints to further demonstrate efficacy are:

- the proportion of patients with a ≥50% reduction from baseline (run-in period) in the weekly average number of CH attacks during the 4-week period after the first dose of the IMP, ie, based on week 0 to 4 data
- the mean change from baseline (run-in period) in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data
- the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat episodic cluster headache (ECH) during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- assessment of patient's perceived improvement, as measured by the Patient-Perceived Satisfactory Improvement (PPSI) at 1, 4, 8, and 12 weeks after administration of the first dose of the IMP relative to baseline (day 0)

1.3. Safety Endpoints

The safety endpoints are as follows:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at each visit
- vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.

- 12-lead electrocardiogram (ECG) findings at screening, baseline, and week 12
- use of concomitant medication during the study
- clinically significant changes in physical examinations, including body weight
- injection site reaction (ie, erythema, induration, and ecchymosis) and injection site pain assessments
- occurrence of hypersensitivity/anaphylaxis reactions
- suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

1.4. Immunogenicity Assessment Endpoints

The immunogenicity endpoints are the following:

- antidrug antibody (ADA) incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

1.5. Exploratory Endpoints

The exploratory endpoints are as follows:

[redacted]

1.6. Wearable Sensor Substudy Endpoints

Wearable sensor substudy exploratory endpoints are the following:

- [redacted]

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a 13-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to compare the safety and efficacy of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of ECH. The study will consist of a screening visit, a run-in period lasting at least 1 week (+3 days), and a 12-week double-blind treatment period. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.

Patients will complete a screening visit (visit 1) after providing written informed consent, and eligible patients will enter a run-in period lasting at least 1 week (+3 days) during which they will enter baseline CH attack information into an electronic diary device (e-diary) daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]). Patients who had at least 7 CH attacks during the run-in period and who continue to meet eligibility criteria (including entry of CH attack information in an e-diary demonstrating compliance for 85% of days during the run-in period) will be randomly assigned at visit 2 (week 0) in a 1:1:1 ratio to 1 of 3 treatment groups (see details in Section 2.2).

Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit for this study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon completion of the final study assessments, early withdrawal from the study, or discontinuation for any reason, patients will be offered the opportunity to enter a 32-week long-term safety study (as described in Study TV48125-CNS-30058) for safety and ADA evaluation without additional dosing.

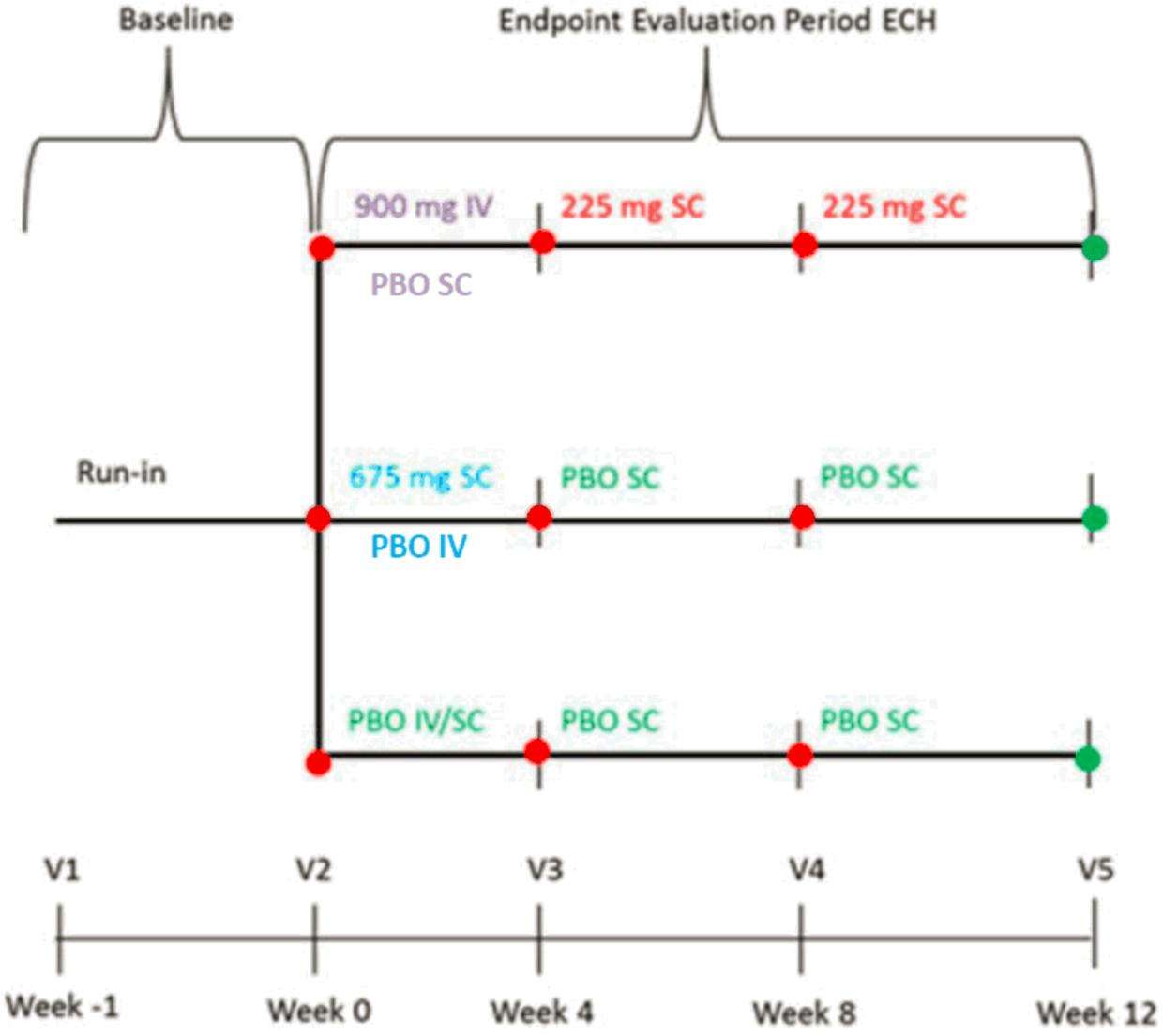
Patients who satisfactorily complete the study may be offered to enroll the long-term safety Study TV48125-CNS-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate. A separate protocol was issued for the long-term safety study.

CH attack information will be captured daily during the double-blind treatment period using an electronic diary device. Assessments of change in quality of life and health status (using the Hospital Anxiety and Depression Scale [HADS], EuroQol-5 Dimension [EQ-5D] questionnaire, 12-Item Short Form Health Survey [SF-12], Impact on Partner and Family questionnaire, and Work Productivity and Activity Impairment [WPAI] questionnaire); satisfaction with treatment (using the PPSI and Patients' Global Impression of Change [PGIC] scale); safety evaluations (including eC-SSRS); blood collection for pharmacokinetics, immunogenicity, biomarker, and pharmacogenomics (unless not allowed per local regulation) analyses; and urine sampling for biomarker analysis will be performed at prespecified time points.

The end of study is defined as the date the last patient attends the end of treatment (EOT)/early withdrawal visit. The study duration will be 21 months from Q4/2016 to Q2/2018.

The study schematic diagram is presented in Figure 1. Study procedures and assessments with their timing are summarized in Table 2 of the study protocol.

Figure 1: Overall Study Schematic Diagram



ECH=episodic cluster headache; IV=intravenous; PBO=placebo; SC=subcutaneous; V=visit. Note: Patients randomized to the 900-mg iv loading dose group will receive 900 mg of fremanezumab administered via an approximately 1-hour iv infusion followed by placebo as 3 sc injections at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively). Patients randomized to the fremanezumab 675-mg sc quarterly group will receive placebo administered via an approximately 1-hour iv infusion followed by fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) and placebo administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively). Patients in the placebo group will receive placebo administered via an approximately 1-hour iv infusion followed by placebo administered as 3 sc injections at visit 2 (week 0) and placebo administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively).

2.1.1. Wearable Sensor Substudy

A subset of patients in selected investigational sites will be offered to participate in a substudy to understand the [redacted]

Patients who are able to demonstrate appropriate use of the wearable device and are willing to comply with the requirements for use of the digital wearable device will be given the device and accessories at the baseline visit. The device will be worn continuously throughout the 12-week treatment period, and for patients who continue into the long-term safety study (Study TV48125-CNS-30058), the device will be worn continuously throughout the 40-week treatment period of that study. Refer to Section 8.6 of the study protocol for additional details.

2.2. Randomization and Blinding

Patients will be randomly assigned with stratification based on gender, country, and baseline concomitant preventive medication use (yes or no) in a 1:1:1 ratio to 1 of 3 treatment groups.

- **fremanezumab 900-mg intravenous (iv) loading dose group**: fremanezumab at 900 mg administered via a 1-hour iv infusion and 3 subcutaneous (sc) placebo injections at visit 2 followed by fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4
- **fremanezumab 675-mg sc quarterly group**: fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) and a 1-hour placebo iv infusion at visit 2 followed by placebo administered as single sc injections at visits 3 and 4
- **placebo group**: placebo administered via a 1-hour iv infusion and as 3 sc injections at visit 2 followed by placebo administered as single sc injections at visits 3 and 4

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses and interim analyses [by a third-party, unblinded statistician]), and patients will be blinded to treatment assignment throughout the study.

Randomization will be performed using electronic interactive response technology (IRT), a third-party vendor. The randomization code will be generated by IRT following 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.

2.3. Data Monitoring Committee

Not applicable.

2.4. Sample Size and Power Considerations

[redacted]

[redacted]

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

An interim analysis for futility evaluation will be performed once 50% of patients (the first 150 patients) have completed 4-week assessments during the double-blind study period or have withdrawn from the study early. An independent statistician from a third party will perform evaluation.

Details are provided in the separate interim analysis plan.

2.5.2. Final Analyses and Reporting

All analyses identified in this SAP will be performed after the final database lock for study completion or for early termination of study as result of futility evaluation at interim analysis.

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. 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, regardless of the treatment to which they were randomized, unless otherwise specified.

3.3. Full Analysis Set

The full analysis set (FAS) will include all patients in the ITT analysis set who receive at least 1 dose of the IMP and have at least 10 days of postbaseline efficacy assessment in the first 4-week 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.

3.4. Per-Protocol Analysis Set

The per-protocol (PP) analysis set will consist of all patients who have completed the study without any violations of the inclusion/exclusion criteria or any violations or omissions of the drug administration.

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

The efficacy analysis for the primary and secondary endpoints will be repeated for the per-protocol analysis set.

3.5. [redacted]

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

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 run-in period (including days from the informed consent up to the day prior to the first dose of the IMP administration) and prorated to 7 days if the number of days in the run-in period is not equal to 7. Details are provided in Section 6.1.

4.3. Region of Pooled Countries

The study is planned to be conducted in approximately 12 countries. The countries will be pooled to 2 regions (US/Canada and other).

4.4. Handling Withdrawals and Missing Data

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

[redacted]

4.5. 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**	**V2**	**V3**	**V4**	**V5**
Week #	**Week -1**	**Week 0**	**Week 4**	**Week 8**	**Week 12**
Visit	**Screening**	**Baseline**	**Visit 3**	**Visit 4**	**EOT/early withdrawal (84 ±3 days)**

Notes: EOT=end of treatment; V2/Week 0 is day 1, which is the day eligible patients are randomized and receive first dose of IMP.

'Last Assessment' may be derived for analysis purpose and is defined as the last observed postbaseline data. For patients who withdraw from the study, their data at the early withdrawal visit will be excluded from the by-visit sections but will be included in the Last Assessment section.

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 first day of the IMP administration and day –1 being the day before the first day of the IMP administration).

For data from the e-diary, weekly analysis windows (week 1, week 2, etc.) and 4-week analysis windows (weeks 1 to 4, weeks 5 to 8, and 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 for all patients.

5.2. Patient Disposition

Data from patients screened; patients screened but not randomized and reason for not randomized; patients who are randomized; patients randomized but not treated; patients in the ITT, safety, and other analysis sets; patients who complete the study; patients who withdraw from the study; and patients continuing into the long-term safety study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

Patients who consent to the wearable sensor substudy and their completion status (completed and reason for not-completed the substudy) will be summarized using descriptive statistics.

This summary will include all patients.

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's demographics data including age, age group (<40 years or ≥40 years), gender, race, race group (white or other), ethnicity, region (US/Canada or other), 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 years since first ECH diagnosis, preventive medication use (yes or no) at screening or baseline, use of any triptans/ergots during the run-in period (yes or no), and number of CH attacks during the run-in period will be summarized for the ITT analysis set [redacted] using descriptive statistics. No inferential analyses will be performed.

[redacted]

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 prior to the administration of the first dose of the IMP.

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

- preventive medication from Appendix H of the study protocol for CH
- preventive medication from Appendix H of the study protocol for other reason than CH
- butalbital for CH
- butalbital for other reason than CH
- triptans for CH
- triptans for other reason than CH
- ergots for CH
- ergots for other reason than CH
- non-steroidal anti-inflammatory drugs (NSAIDs) for CH
- NSAIDs for other reason than CH
- opioids for CH
- opioids for other reason than CH
- 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 [redacted].

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 run-in period (including days from the informed consent up to the day prior to the first dose of the IMP administration). Details are provided in Section 6.1.3. The efficacy baseline value derived from the run-in period are

- number of CH attacks
- number of CH attacks of at least severe severity
- number of days with use of cluster-specific acute headache medication (triptans and ergot compounds)
- number of days with use of any acute headache medication
- number of days oxygen is used
- severity of CH attacks

Summaries will be presented by treatment group as randomized unless otherwise noted. In addition to inferential statistics, descriptive statistics will be presented by-visit or by-analysis-window summaries.

6.1.1. Cluster Headache Attacks Data from E-diary

[redacted]

6.1.2. Data Derivation

The ***weekly average/value*** of an efficacy endpoint will be calculated and prorated to 7 days as follow:

$$\frac{\sum efficacy\ endpoint\ data\ during\ the\ period}{Number\ of\ Days\ with\ assessments\ recorded\ in\ the\ eDiary\ during\ the\ period} \times 7 \quad [1]$$

The "efficacy endpoint data" will be "number of CH attacks", "days with use of cluster-specific acute headache medications (tripants and ergot compounds)", "days oxygen is used to treat ECH", or "days with use of any headache medication", etc.

The period will be the run-in period (including days from the informed consent up to the day prior to the first dose of the IMP administration) for baseline calculation or an analysis window (eg. weeks 1 to 4, weeks 5 to 8, weeks 9 to 12, etc.) for post-baseline calculations.

[redacted]

6.1.3. Analysis Windows for E-diary Data

Baseline window is the run-in period and includes days from the informed consent to the day prior to the first dose of the IMP administration. The baseline weekly average value for an efficacy variable will be calculated based on data recorded in the run-in period and prorated to 7 days using formula [1].

Note, per eligibility checks at visit 2, patients with more than 10 days in the run-in period will not be eligible and will not be randomized for the study. However, in case there are patients with more than 10 days of the e-diary data collected during the run-in period, all data will be used for the baseline calculation by prorating the data to 7 days.

[redacted]

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.

6.1.4.1. Primary Efficacy Endpoint

The weekly average number of CH attacks during the 4-week period will be calculated based on data available and prorated to 7 days using formula [1]. Note, patients who have < 10 days of e-diary data in the first 4-week will be excluded from FAS and PP analysis set (Section 3).

As sensitivity analyses, the primary endpoint will be analyzed using the following methods for handling missing data :

- Multiple imputation (MI) method to impute missing weekly data
- An mixed model for repeated measures (MMRM) method to analyze the weekly data

Detail is provided in Section 6.2.3.

6.1.4.2. Analyses Based on Monthly and 12-week Window

[redacted]

6.2. Primary Efficacy Endpoint and Analysis

6.2.1. Definition

The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the weekly average number of CH attacks during the 4-week period after administration of the first dose of the IMP.

CH attacks will be derived from the e-diary data as described in Section 6.1.1. The analysis will be based on the weeks 1 to 4 analysis window, which will be derived using the algorithm described in Section 6.1.3. Missing data handling methods are provided in Section 6.1.4.1.

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 δ_1 and δ_2 are the estimates of mean change from baseline in the weekly average number of CH attacks for the fremanezumab treatment group and the placebo group, respectively. To

control overall type I error rate, the comparison of each active treatment group (fremanezumab 900-mg iv loading dose group and fremanezumab 675-mg sc quarterly group) versus the placebo will be tested using Hochberg's step-up method as described in Section 7.

The primary endpoint will be analyzed using an ANCOVA method. The model will include baseline preventive medication use (yes or no), gender, region (US/Canada or other), and treatment as fixed effects; the baseline number of CH attacks as a covariate. 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 set,

6.2.3. Sensitivity Analyses for the Primary Efficacy Endpoint

Sensitivity analyses will be conducted to explore the impact of missing data in the primary efficacy analysis.

6.2.3.1.

.

[redacted]

The analysis will be performed on the ITT analysis set.

6.2.3.2. Mixed Model for Repeated Measures Analysis

MMRM analysis will be utilized to estimate the mean change from baseline in the weekly number of CH attacks during the 4-week period after administration of the first dose of the IMP.

Postbaseline data will include data from four 1-week analysis windows derived using the algorithm described in Section 6.1.3. Missing data will be handled as described in Section 6.1.4.3

The MMRM will include baseline preventive medication use (yes or no), gender, region (US/Canada or other), treatment, week (weeks 1 to 4), and week-by-treatment interaction as fixed effects and baseline number of CH attacks 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 weeks 1 to 4 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).

[redacted]

The analysis will be performed on the FAS.

6.2.4. Exploratory Analysis

As an exploratory analysis, [redacted]. The overall results will be presented.

6.2.5. [redacted]

[redacted]

[redacted]

6.3. Secondary Efficacy Endpoints and Analyses

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

As exploratory analyses, endpoints analyzed using an ANCOVA method will be also analyzed using MMRM method in a manner analogous to the analysis as described in Section 6.2.3.2. The analysis windows will be specified in the related section.

6.3.1. Proportion of Patients with a ≥50% Reduction from Baseline in the Weekly Average Number of CH Attacks During the 4-Week Period After the First Dose of the IMP

This secondary efficacy endpoint will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by baseline preventive medication use (yes or no). Descriptive statistics (count and percent) and p-value for Row Mean Scores difference will be presented.

CH attacks will be derived from the e-diary data as described in Section 6.1.1. The analysis will be based on weeks 1 to 4 analysis window which will be derived using the algorithm described in Section 6.1.3. The weekly average number of CH attacks will be calculated based on data available and prorated to 7 days using formula [1]. Missing data handling methods are provided in Section 6.1.4.2.

The proportion of reduction for a patient will be calculated using formula [2]. Responders will be those with ≥50% reduction.

[redacted]

6.3.2. Mean Change from Baseline in the Number of Cluster Headache Attacks

The following 2nd and 3rd secondary efficacy endpoints will be analyzed using an MMRM method in a manner analogous to the analysis as described in Section 6.2.3.2 with month and month-by-treatment interaction in the model instead.

- the mean change from baseline (run-in period) in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data

Postbaseline data will include data from three 4-week analysis windows (weeks 1 to 4, weeks 5 to 8, and weeks 9 to 12) derived using the algorithm described in Section 6.1.3. CH attacks within each analysis window will be derived from the e-diary data as described in Section 6.1.1. The weekly average of number of CH attacks for a patient in each analysis window will be calculated and prorated to 7 days using formula [1]. Missing data handling methods are provided in Section 6.1.4.2.

The analysis will be based on data from all three 4-week analysis windows. Results for each endpoint will be subsetted from PROC MIXED outputs. For the 2nd secondary endpoint, the overall results will be presented; for the 3rd secondary endpoint, the results from the weeks 9 to 12 analysis window will be presented.

6.3.3. Mean Change from Baseline in the Weekly Average Number of Days with Use of Cluster-Specific Acute Headache Medications (Triptans and Ergot Compounds) During the 12-Week Period After Administration of the First Dose of the IMP

Use of triptans and ergot compounds for CH will be recorded in the e-diary. The 12-week period is the period from administration of the first dose of the IMP to the EOT/early withdrawal visit. The weekly average number of days with use of triptans or/and ergots for CH for a patient during 12-week period will be calculated and prorated to 7 days using formula [1]. Missing data handling method is provided in Section 6.1.4.2.

Data will be analyzed using an ANCOVA method in a manner analogous to the primary endpoint as described in Section 6.2.2.

MMRM analysis will be based on weekly analysis windows. Data in weekly analysis windows will be derived.

6.3.4. Mean Change from Baseline in the Weekly Average Number of Days Oxygen is Used to Treat Episodic Cluster Headaches During 12-week Period After Administration of the First Dose of the IMP

Use of oxygen will be recorded in the e-diary. The 12-week period is the period from administration of the first dose of the IMP to the EOT/early withdrawal visit. The weekly average number of days using oxygen for a patient during the 12-week period will be calculated and prorated to 7 days using formula [1]. Missing data handling method is provided in Section 6.1.4.2.

Data will be analyzed using an ANCOVA method in a manner analogous to the primary endpoint as described in Section 6.2.2.

MMRM analysis will be based on weekly analysis windows. Data in weekly analysis windows will be derived.

6.3.5. Patient-Perceived Satisfactory Improvement at 1, 4, 8, and 12 Weeks After Administration of the First Dose of the IMP Relative to Baseline

The PPSI scale will be completed in the e-diary at home at week 1 (day 7) and in the investigational site tablet at the visits 2, 3, 4, and 5. Patients will mark the level of CH-associated pain and indicate the level of pain using the following scale compared with 4 weeks ago:

- 1 = Much worse
- 2 = Moderately worse
- 3 = Slightly worse
- 4 = Unchanged
- 5 = Slightly improved
- 6 = Moderately improved
- 7 = Much improved

PPSI will be defined as change in pain that corresponds with a minimal rating of "slightly improved" (Protocol Section 6.7). For analysis purpose, a dichotomous scale of "Responder" (scales 5 to 7) or "Non-responder" (scales 1 to 4) will be derived.

The percentage of patients in dichotomous scale of "Responder" or "Non-responder" at week 1, visit 3, 4, and 5 will be analyzed using a CMH method in a manner analogous to the first secondary endpoint as described in Section 6.3.1. Missing scores will not be imputed.

Modification to SAS code in Section 6.3.1: adding a 'by' statement for visit.

Raw scales will be summarized using descriptive statistics. A missing category will be presented if applicable.

6.4. Exploratory Efficacy Endpoints and Analysis

Exploratory efficacy endpoints are listed in Section 1.5. [redacted].

[redacted]

Section 6.2.3.2. The analysis windows will be specified in the related section.

6.4.1. [redacted]

The following exploratory efficacy endpoints will be analyzed [redacted]

- [redacted]

[redacted]

6.4.2. Mean Change from Baseline in the Number of CH Attacks During Weeks 1, 2, 3, [redacted]

[redacted]

6.4.3. [redacted]

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6.4.4. [redacted]

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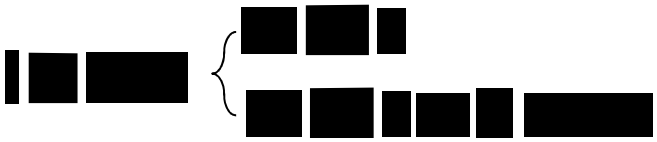

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6.4.7. [redacted]

The derivation of input data for this analysis is the same as the primary analysis except only [redacted]

6.4.8. [redacted]

6.4.8.1. [redacted]

6.4.8.2. [redacted]

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6.4.8.6. [redacted]

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7. MULTIPLE COMPARISONS AND MULTIPLICITY

[redacted]

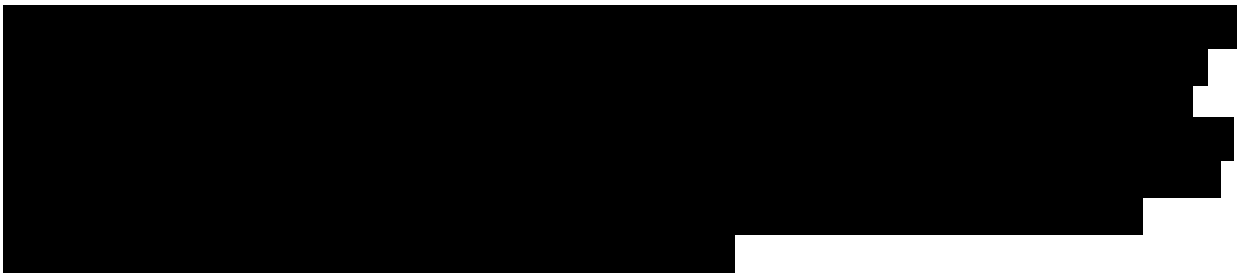
8. SAFETY ANALYSIS

8.1. General

The safety analysis set will be used for all safety analyses. Summaries will be presented using descriptive statistics by treatment group and all fremanezumab as actually received unless otherwise stated.

8.2. Duration of Exposure to Study Drug

At the visit 2, each patient will receive a 1-hour iv infusion and 3 sc injections of fremanezumab or placebo. At visits 3 and 4, patients will receive 1 sc injection of fremanezumab or placebo.



Duration of the treatment period (days), duration of iv infusion (minutes), dosing visit interval (days), the number of doses received, total number of injections received (placebo or fremanezumab), and reasons for IMP not administrated will be summarized using descriptive statistics. Summary will be presented by treatment group.

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 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 (aspartate aminotransferase or alanine aminotransferase ≥3 × the upper limit of normal [ULN], total bilirubin ≥2 × the ULN, or international normalized ratio >1.5), Hy's Law events, or events of anaphylaxis and severe hypersensitivity reactions.

All adverse events will be coded using MedDRA (version 18.1). 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 and by severity), serious adverse events, 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 and infusion-related adverse events and protocol-defined adverse events of special interest will be presented (overall and by severity).

Listings for deaths, serious adverse events, adverse events leading to discontinuation, injection site and infusion-related adverse events, and protocol-defined adverse events of special interest 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 site(s) will be assessed for erythema, induration, and ecchymosis. More details are in Section 7.11 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 reaction during and after administration of the IMP (through 1 hour postdose) at visits 2, 3, and 4. Data will be summarized using descriptive statistics.

The number of patients with suspected anaphylaxis reactions and number of suspected anaphylaxis 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 M) will be performed at all visits (visit 1 [screening] through visit 5 [EOT]) 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 and Last Assessment will be summarized using descriptive statistics. Shifts (below [low], within [normal], and above [high] the normal range) from baseline to each postbaseline visit 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 ≥20 x 10^9/L
Eosinophils		≥10%
ANC		≤1 x 10^9/L
Platelet counts		≤75 x 10^9/L ≥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

Serum beta-human chorionic gonadotropin (β-HCG) tests will be performed for all women of childbearing potential at visits 1 and 5. Urine β-HCG tests will be performed for women of childbearing potential at visits 2 through 4. Pregnancy test results will be listed.

Current menstruating status (yes or no) will be collected at all visits and 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 at each (visit 1 through 5). Weight will be measured at visits 1, 2, and 5. 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 and the Last Assessment 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 visits 1, 2, and 5. 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 the 3 measurements at a visit will be calculated. The mean results and mean changes from baseline to EOT and Last Assessment 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 (also see Section 4.2).

For ECG findings, the worst value of recorded 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 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 collected up to the end of 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

Tolerability was not specifically defined for this study.

10. PHARMACOKINETIC ANALYSIS

There are no prespecified pharmacokinetic endpoints.

Fremanezumab plasma concentration will be summarized using descriptive statistics at each planned sampling time point for each of the active treatment groups (samples from patients who received placebo will not be analyzed). The summary will be based on the safety analysis set. The plasma concentration will be listed by active treatments, scheduled visits and time points.

11. PHARMACOGENOMIC ANALYSIS

Pharmacogenomic analysis results will be summarized for each gene tested. An attempt will be made to correlate clinical observations (pharmacokinetics, safety, efficacy, or other effects) with the genotypes observed. Additional pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

This analysis is not included in this SAP.

12. BIOMARKER ANALYSIS

Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. Results will be reported separately. Measurements will be made using validated assays.

This analysis is not included in this SAP.

13. IMMUNOGENICITY ANALYSIS

A summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetics profile, IMP efficacy, and clinical safety will be evaluated. This ADA impact analysis will be reported separately.

This analysis is not included in this SAP.

14. ANCILLARY STUDY ANALYSIS – WEARABLE SENSOR SUBSTUDY

A subset of patients (n=45, approximately 15 patients from each treatment group) from each pivotal study (TV48125-30056 and TV48125-30057), approximately 90 patients in total, will be asked to wear a sensor monitoring system (digital wearable device) on the wrist to track sleep patterns and activity patterns. These patients will be allowed to continue in the substudy during the long-term safety study (TV48124-30058).

Analyses for endpoints from the wearable sensor substudy will include summary statistics and [redacted] Results will be reported separately.

15. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS®.

16. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

None.

17. 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.

APPENDIX A. [redacted]

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