STATISTICAL ANALYSIS PLAN

A multicenter, open-label trial to evaluate the safety of TEV-48125 when subcutaneously self-administered in migraine patients at the trial site and at home

NCT Number: NCT04355117

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
TEV-48125

Protocol No. 406-102-00005

A multicenter, open-label trial to evaluate the safety of TEV-48125 when subcutaneously self-administered in migraine patients at the trial site and at home

Statistical Analysis Plan

Version: 1.0
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
AI	Autoinjector
AE	Adverse event
CM	Chronic migraine
ECG	Electrocardiogram
eDiary	Electronic headache diary
EM	Episodic migraine
EOT	End of Treatment
EAS	Efficacy Analysis Set
ICHD-3	The International Classification of Headache Disorders, 3rd edition
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
PK	Pharmacokinetic
PT	Preferred Term
QTcB	QT corrected for heart rate by Bazett's formula
QTcF	QT corrected for heart rate by Fridericia's formula
SAP	Statistical Analysis Plan
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent adverse event

1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy, safety and pharmacokinetic data of Trial 406-102-00005. Analysis of immunogenicity is described in the bioanalytical protocol. All amendments to the protocol are taken into consideration in developing the SAP.

2 Trial Objective

The primary objective is to assess the safety of TEV-48125 (generic name: fremanezumab) when subcutaneously self-administered in Japanese migraine patients using an autoinjector (AI) at home.

3 Trial Design

3.1 Type/Design of Trial

This trial is a multicenter, open-label trial in migraine patients. The schematic of the trial design is shown in Figure 3.1-1 and trial assessment time points are summarized in the protocol Table1.3-1.

The trial will consist of a 4-week screening period and an 8-week treatment period.

After obtaining written informed consent from each subject, the investigator will screen the subject for eligibility (Visit 1/Screening). On each day during the screening and the treatment periods, subjects are to enter headache data in the electronic headache diary (eDiary) provided for use in this trial.

By Visit 2/Baseline, the investigator will provide subjects who have been diagnosed with migraine and who meet all the inclusion criteria and do not fall under any of the exclusion criteria with sufficient instruction on self-administration using the “Procedure for TEV-48125 AI Self-administration.” At Visit 2/Baseline subjects for whom the investigator judges self-administration to be possible in compliance with the procedure will perform self-administration using the AI at the trial site under the supervision of the investigator.

The investigator will confirm whether the subject is able to perform self-administration in compliance with the procedure, and judge whether self-administration at home is possible. Subjects for whom the investigator judges self-administration at home to be possible will perform self-administration using the AI at home after performing protocol-specified procedures at Visit 3. Subjects will be asked to visit the trial site for blood sampling for plasma drug concentration measurement at 3 to 10 days after investigational

medicinal product (IMP) administration at Visit 2/Baseline and Visit 3. At 4 weeks after final IMP administration (self-administration at home) subjects will visit the trial site for the final evaluation (Visit 4/End of Treatment [EOT]). For subjects who are withdrawn from the trial, a withdrawal examination will be performed wherever possible.

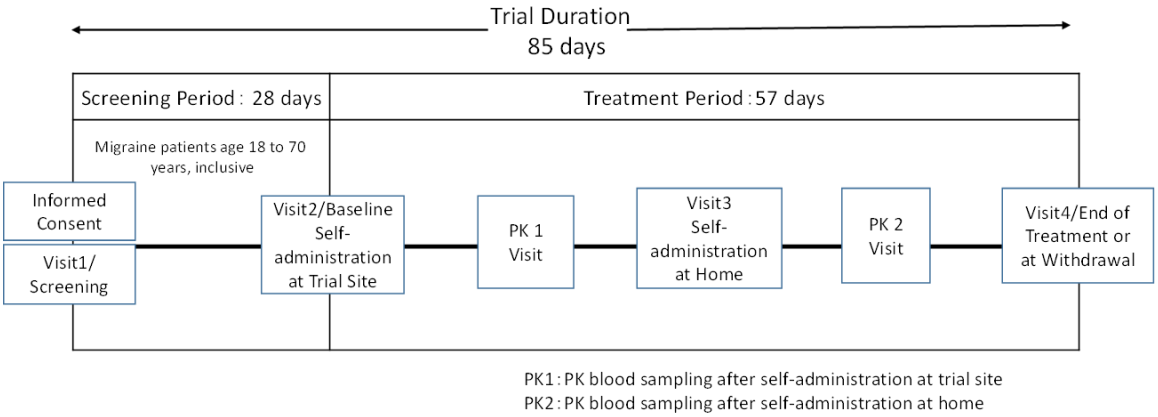

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

In this trial, each subject will subcutaneously self-administer TEV-48125 at 225 mg/1.5 mL (150 mg/mL) once monthly for a total of 2 doses. The first dose will be self-administered at the trial site under the supervision of the investigator and the second dose will be self-administered at home. The injection site may be the back of the upper arm, the abdomen, or the front of the thigh. To the extent possible, the injection site should be the same for both doses (but not exactly in the same location).

3.3 Trial Population

Migraine patients age 18 to 70 years, inclusive, who have a history of migraine (The International Classification of Headache Disorders, 3rd edition [ICHD-3] criteria [see Section 10.4 in the protocol]) or for whom clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to giving informed consent.

Subjects who are using preventive migraine medications (see Table 6.5.2-1 List of Restricted Concomitant Medications [Preventive Migraine Medications] in the protocol) will be permitted to continue using no more than 2 preventive migraine medications only

if the dose and regimen have been stable for at least 2 months prior to screening examination (Visit 1/Screening).

4 Sample Size

The statistically required sample size based on power was not calculated. The sample size for evaluating the safety of TEV-48125 when subcutaneously self-administered at the trial site and at home was set at 50 subjects.

5 Statistical Analysis Sets

5.1 Safety Set

The safety set (SS) includes all subjects who received at least one dose of IMP.

5.2 Efficacy Analysis Set

The efficacy analysis set (EAS) includes all subjects who received at least one dose of IMP and have eDiary data for efficacy evaluation at baseline and for at least 10 days after baseline.

5.3 Handling of Missing Data

Missing data will not be imputed.

6 Primary and Other Outcome Variables

The primary objective is to assess the safety of TEV-48125 when subcutaneously self-administered in Japanese migraine patients using an AI at home.

The primary endpoint of the trial is the occurrence of adverse events (AEs), and the safety of the IMP will be assessed based on the occurrence of AEs. Other endpoints will include evaluation of the execution status of self-administration at home and subject compliance with the self-administration procedure, and an overall evaluation of the feasibility of self-administration of TEV-48125 at home. In addition, as the IMP is a combination product, any deficiencies with the AI device will also be evaluated.

As exploratory endpoints, efficacy parameters including the number of migraine days, the number of headache days, and the number of headache days of at least moderate severity will be evaluated.

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of subjects from whom informed consent has been obtained and the number of screen failure subjects and of enrolled subjects who are judged to be eligible will be summarized. For the enrolled subjects, the number and percentage of subjects in whom IMP is administrated, in whom IMP is not administrated, who completed the trial, who are withdrawn from the trial will be summarized. The primary reason for discontinuation will also be summarized. The number and percentage of subjects who are included in the SS and EAS, and who are excluded from the SS and EAS will be summarized.

7.2 Judgment on Self-administration

For the enrolled subjects, frequency distributions for judgment on self-administration at the trial site and at home will be summarized.

7.3 Demographic and Baseline Characteristics

Data will be summarized for the enrolled subjects.

The following demographic and baseline characteristics will be summarized. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum; hereinafter the same applies). Categorical variables will be summarized using the number and percentage of subjects.

- Age (≤45, ≥46 to ≤64, ≥65), sex (male, female)
- Country, ethnicity, detailed ethnicity, race
- Weight at screening, height, body mass index
- Use of preventive migraine medication at baseline (yes, no)
- Years since onset of migraines

Medical history and complications will be coded by system organ class (SOC) and Medical Dictionary for Regulatory Activities (MedDRA Version 23.1) preferred term (PT). The number and percentage of subjects with medical history and complications will be summarized by SOC and PT for the enrolled subjects. Subjects are counted only once in each SOC and only once in each PT.

7.4 Baseline Disease Evaluation

Data will be summarized for the enrolled subjects.

The following baseline disease evaluation will be summarized. Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using the number and percentage of subjects.

- Migraine subtype
- Number of headache days of any duration and any severity
- Number of migraine days
- Number of headache days of at least moderate severity

Migraine subtype (chronic migraine [CM] or episodic migraine [EM]) will be determined based on the eDiary data during the 28-day screening period (from Day −28 to Day −1). Criteria for CM and EM are defined as follows.

[EM]
– Headache days: ≥ 4 and ≤ 14 days
– Migraine days: ≥ 4 days
[CM]
– Headache days: ≥ 15 days
– Migraine days: ≥ 8 days
Subjects who do not meet the criteria for CM and EM will be classified as “Other”.

The baseline value will be calculated using all data collected from the day of V1/Screening through the day before V2/Baseline and normalized to 28 days (ie, if the number of days from V1/Screening through the day before V2/Baseline is greater or less than 28 days, the baseline value will be normalized to 28 days, see Section 13.1.1) using the electronic headache diary data collected through the corresponding headache diary questions.

7.5 Treatment Compliance

The information for self-administration of IMP is described in Section 9.3.

7.6 Prior and Concomitant Medications

Data will be summarized for the enrolled subjects.

All prior and concomitant medications collected via case report form will be coded using the World Health Organization dictionary of medical codes (WHO Drug Dictionary Global B3 March 2020). The number and percentage of subjects with prior medications and concomitant medications will be summarized by medication class and preferred name. Subjects are counted only once in each medication class category, and only once in each preferred name category. Prior medications will include all medications taken prior

to the first dose of IMP. Concomitant medications will include all medications taken after the first dose of IMP.

The subset of prior medications and concomitant medications will be summarized for the following categories.

- Prohibited and restricted medications for preventive treatment of migraine medication
- Triptans and ergots for treatment of acute migraine
- Non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of acute migraine
- Opioids for treatment of acute migraine

Additionally, the number and percentage of subjects with restricted concomitant medications (preventive treatment of migraine medications, Table 6.5.2-1 in the protocol) used at baseline will also be summarized.

7.7 Protocol Deviations

The number and percentage of subjects with any major protocol deviations and each classification will be provided in each trial site and overall site for enrolled subjects.

8 Efficacy Analyses

The information for efficacy analyses is described in Section 13.

9 Safety Analyses

The SS will be used for all safety analyses. Descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

9.1 Extent of Exposure

Duration of treatment (days treated) is the number of days on treatment based on the first dose of IMP day and EOT visit day/early withdrawal day (EOT visit day – first day of IMP + 1). For subjects who are lost to follow-up, the EOT date is defined as the last dose of IMP date + 27. The number of subjects receiving ≥1 dose and ≥2 doses will be summarized. Duration of treatment (days) will be summarized using descriptive statistics and frequency distribution for the cumulative categories (>0 months, ≥1 month, and ≥2 months). One month will be defined as 28 days. The total exposure of IMP allocated at each administration will also be summarized.

9.2 Adverse Events

All AEs will be coded by SOC and MedDRA PT. The incidence of the following events will be summarized for overall treatment period, self-administration at trial site (at the time of or after the self-administration at trial site to before the self-administration at home), and self-administration at home (at the time of or after the self-administration at home to the end of study):

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs reported in at least 2% of subjects

The above summaries will also be prepared for TEAEs potentially causally related to TEV-48125, TEAEs potentially causally related to AI device, and TEAEs potentially causally related to the subject's manipulation. In addition, the following TEAEs will be tabulated.

- Injection site reaction TEAEs
  Injection site reaction AEs are determined by the investigator.
- Ophthalmic TEAEs of at least moderate severity
  Ophthalmic AEs are defined as coded Eye disorders (10015919) by SOC.
- Drug-related Hepatic TEAEs
  Drug-related hepatic AEs will be captured using the standardized MedDRA query (SMQ) Drug related hepatic disorders - comprehensive search (20000006).
- Anaphylaxis and severe hypersensitivity reaction TEAEs
  Anaphylaxis and severe hypersensitivity reaction AEs will be captured using the SMQ Hypersensitivity (20000214).
- Cardiovascular-related TEAEs
  Cardiovascular-related AEs will be captured using the SMQ Central nervous system vascular disorders (20000060), Cardiac arrhythmias (20000049), Cardiac failure (20000004), Cardiomyopathy (20000150), Ischaemic heart disease (20000043), Hypertension (20000147), Torsade de pointes/QT prolongation (20000001), and coded Vascular disorders (10047065) by SOC.
- Non-serious TEAEs reported in at least 5% of subjects

9.3 Execution Status of Self-administration and Subject Compliance With Self-administration Procedure

Frequency distributions will be determined by location (at trial site or at home) for the execution status of self-administration and subject compliance with the self-administration procedure.

Frequency distributions for the execution status of self-administration and subject compliance with self-administration procedure will be summarized for self-administration at trial site and for self-administration at home. Status of leakage of drug solution on the skin after subcutaneous injection will also be summarized using dichotomized categories (0 to 2 and 3 to 4) of the descriptions.

9.4 Deficiencies With the Autoinjector Device

Deficiencies with the AI device will be listed.

9.5 Clinical Laboratory Data

Descriptive statistics will be calculated for clinical laboratory data and changes from baseline at each time point (Baseline, V3/Month 1, V4/Month 2, and final evaluation).

Frequency distributions with the numbers and percentages of subjects with potentially clinically significant (PCS) values with any post-baseline (including unscheduled assessments and final evaluation) will be presented. The denominator for calculating the percentage of subjects will be the number of subjects with at least one post-baseline result for each test. Listing of subjects with PCS values will be prepared. The criteria are presented in Appendix 1.

For clinical laboratory items, other than qualitative urinalysis, the baseline and post-baseline values will be assessed as normal, high, or low, based on the reference range, and shift tables of those values will be prepared for each time point.

Baseline value will be the last value prior to the first dose of IMP. Each time point for post-baseline will be the nominal visits. Final evaluation will be based on the last observed post-baseline data (including scheduled, unscheduled, and withdrawal visits). Summaries of PCS values will include all post-baseline data.

9.6 Vital Sign and Weight Data

Descriptive statistics will be calculated for vital sign and weight measurements and changes from baseline at each time point (Baseline, V3/Month 1, V4/Month 2, and final evaluation).

Frequency distributions with the numbers and percentages of subjects with PCS values with any post-baseline (including unscheduled assessments and final evaluation) will be presented. The denominator for calculating the percentage of subjects will be the number of subjects with at least one post-baseline result for each test item. Listing of subjects with PCS values will be prepared. The criteria are presented in Appendix 2.

Baseline value will be the last value prior to the first dose of IMP. Each time point for post-baseline will be the nominal visits. Final evaluation will be based on the last observed post-baseline data (including scheduled, unscheduled, and withdrawal visits). Summaries of PCS values will include all post-baseline data.

9.7 Physical Examination Data

A listing of physical examination findings will be prepared for each subject.

9.8 Electrocardiogram Data

Descriptive statistics will be calculated for electrocardiogram (ECG) measurements and changes from baseline at each time point (Baseline, V3/Month 1, V4/Month 2, and final evaluation). Shift tables will be created for baseline vs post-baseline assessment results (normal, abnormal not clinically significant, or abnormal clinically significant) at final evaluation vs worst value at any time point.

For QTcB and QTcF, frequency distributions with the numbers and percentages of subjects will be presented for the following criteria:

- Subject with a value of >450 msec post-baseline*
- Subject with a value of >480 msec post-baseline*
- Subject with a value of >500 msec post-baseline*
- Subject with prolongation from baseline of >30 msec at post-baseline*
- Subject with prolongation from baseline of >60 msec at post-baseline*

  * “post-baseline” in the above criteria are at final evaluation and worst value.

Baseline value will be the last value prior to the first dose of IMP. Each time point for post-baseline will be the nominal visits. Final evaluation will be based on the last observed post-baseline data (including scheduled, unscheduled and withdrawal visits). Worst value will be derived using all post-baseline data.

9.9 Other Safety Data

9.9.1 Injection Site Reactions

For severities of the injection site reactions (erythema, induration, ecchymosis, and pain), frequency distributions will be obtained by IMP administration visit (V2/Self-administration at the Trial Site and V3/Self-administration at Home) and time point (immediately postdose and 1 hour postdose).

9.9.2 Columbia-Suicide Severity Rating Scale

A listing of subjects showing suicidal ideation or behavior, evaluated based on the C-SSRS results, will be prepared.

10 Pharmacokinetic Analyses

Not applicable.

11 Pharmacodynamic Analyses

Not applicable.

12 Pharmacogenomic Analyses

Not applicable.

13 Exploratory Endpoints

For the EAS, descriptive statistics of values and changes from baseline in the monthly average number of migraine days during the 8-week period after the first dose of IMP and during the 4-week period after each dose will be summarized. The same analysis will be performed for the number of headache days of at least moderate severity and the number of headache days of any severity.

Proportion of subjects reaching at least 50% reduction in the monthly average number of migraine days during the 8-week period after the first dose of IMP and during the 4-week period after each dose will be summarized. The same analysis will be performed for number of headache days of at least moderate severity.

13.1.1 Technical Computational Details for Headache-Related Data

- Definition of migraine day
  A migraine day for CM subjects is defined as when at least one of the following situations occurs:

  - A calendar day (0000 to 2359) with at least 4 consecutive hours of headache meeting the criteria for migraine with or without aura
  - A calendar day (0000 to 2359) with at least 4 consecutive hours of headache meeting the criteria for probable migraine, a migraine subtype where only one migraine criterion is missing
  - A calendar day (0000 to 2359) with a headache of any duration that was treated with migraine-specific medication (triptans and ergot compounds)

  A migraine day for EM and other subjects is defined as when at least one of the following situations occurs:

  - A calendar day (0000 to 2359) with at least 2 consecutive hours of headache meeting the criteria for migraine with or without aura
  - A calendar day (0000 to 2359) with at least 2 consecutive hours of headache meeting the criteria for probable migraine, a migraine subtype where only one migraine criterion is missing
  - A calendar day (0000 to 2359) with a headache of any duration that was treated with migraine specific-medication (triptans and ergot compounds)

  The derivation logic is presented in Appendix 3.

- Definition of headache day of at least moderate severity

  A headache day of at least moderate severity is defined as when at least one of the following situations occurs:

  - A calendar day (0000 to 2359) with headache pain that lasts ≥4 hours with a peak severity of at least moderate severity
  - A calendar day (0000 to 2359) when the subject used acute migraine-specific medication (triptans or ergots) to treat a headache of any severity or duration

- Definition of headache day of any severity

  The headache day of any severity is defined as a calendar day (0000 to 2359) with headache pain that lasts ≥4 hours of any severity or a day when the subject used acute migraine-specific medication (triptans or ergots) to treat headache of any severity or duration.

- Variable definitions

  The baseline value will be calculated using all data collected from the day of V1/Screening through the day before V2/Baseline and normalized to 28 days (ie, if the number of days from V1/Screening through the day before V2/Baseline is greater or less than 28 days, the baseline value will be normalized to 28 days; see the following formula).

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ screening\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ screening\ period} \times 28$$

  The monthly average number of efficacy endpoints (eg, migraine days, headache days of at least moderate severity, etc.) during the 8-week period after the first dose of IMP will be derived and normalized to 28 days (see the following formula), if a subject has ≥10 days of electronic headache diary data after the first dose of IMP.

$$\frac{\sum Days\ of\ efficacy\ variable\ over\ the\ 8\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 8\ week\ period} \times 28$$

The monthly number of days of efficacy endpoints (eg, migraine days, headache days of at least moderate severity, etc.) during a 4-week period after each dose at Visits 2 and Visit 3 (ie, for Months 1 and Month 2) will be derived and normalized to 28 days (see the following formula), respectively. If a subject is withdrawn early or has intermittent missing days and has <10 days of electronic headache diary entries for a month, that month's value will be considered as missing.

$$\frac{\sum Days\ of\ efficacy\ variable\ over\ the\ 4\ week\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 4\ week\ period} \times 28$$

14 Plasma Drug Concentration

For the SS, descriptive statistics will be calculated for measured values at each sampling time point for plasma drug concentration. Box-plot and scatter plot for measured values will be provided.

15 Interim Analysis

None.

16 Changes in the Planned Analyses

The categorical analysis for QTcB is added in Section 9.8.

17 References

None.

Appendix 1 Criteria for Identifying Potentially Clinically Significant Laboratory Values

Laboratory Tests	Criteria
Serum chemistry	
Alanine aminotransferase	≥ 3 x upper limit of normal
Aspartate aminotransferase	≥ 3 x upper limit of normal
Alkaline phosphatase	≥ 3 x upper limit of normal
Gamma glutamyl transferase	≥ 3 x upper limit of normal
Lactate dehydrogenase	≥ 3 x upper limit of normal
Urea Nitrogen	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Total bilirubin	≥ 2.0 mg/dL
Coagulation	
International normalized ratio	> 1.5
Hematology	
Hematocrit	
Male	< 37 %
Female	< 32 %
Hemoglobin	
Male	≤ 11.5 g/dL
Female	≤ 9.5 g/dL
Leukocytes count	≤ 3,000 uL or ≥ 20,000/ uL
Eosinophils	≥ 10%
Neutrophils	≤ 1,000 uL
Platelet count	≤ 7.5 10^4/uL or ≥ 70 10^4/uL
Urinalysis	
Occult blood	≥ 2 units increase from baseline
Glucose	≥ 2 units increase from baseline
Ketones	≥ 2 units increase from baseline
Protein	≥ 2 units increase from baseline

Appendix 2 Criteria for Identifying Potentially Clinically Significant Vital Signs

Variable	Criterion Value	Change Relative to Baseline
Pulse Rate	≥ 120 beats/min ≤ 50 beats/min	Increase of ≥ 15 beats/min Decrease of ≥ 15 beats/min
Systolic Blood Pressure	≥ 180 mmHg ≤ 90 mmHg	Increase of ≥ 20 mmHg Decrease of ≥ 20 mmHg
Diastolic Blood Pressure	≥ 105 mmHg ≤ 50 mmHg	Increase of ≥ 15 mmHg Decrease of ≥ 15 mmHg
Respiratory Rate	< 10 breaths/min	-
Body Temperature	≥ 38.3°C	Change of ≥ 1.1°C

Appendix 3 Logics for Migraine Day Derivation

Migraine Day will be 1 of the following 4 options.

Option 1: Part 1 met and at least 2 of the Part 2 met and at least 1 of the Part 3 met

Option 2: A1 = Yes and D3 = Yes (medication were “Ergot” or “Triptan”)

Option 3: A1 = Yes and “B7 = Yes and/or B8 = Yes”

Option 4 (Probable Migraine):

-Part 1 met and at least 2 of the Part 2 met, and only one of met in “B5 = Yes or B6 = Yes”

-Part 1 met and at least 1 of the Part 3 met, and only one of met in Part 2

-At least 2 of the Part 2 met, at least 1 of the Part 3 met, and A1 = Yes

Part	Electronic Headache Diary Questionnaire	
Part 1	1	A1 = Yes
	2 for CM subjects	A2 = Yes
	2 for EM and other subjects	A2 = Yes or A3 = Yes
Part 2	1	A4 = Moderate or Severe
	2	B1 = Yes
	3	B2 = Yes
	4	B3 = Yes
Part 3	1	B4 = Yes
	2	B5 = Yes and B6 = Yes

CM = Chronic migraine; EM = Episodic migraine

Electronic Headache Diary Questionnaire

A1	Did you experience a headache of any severity yesterday?
A2	Did you have at least four (4) consecutive hours of headache yesterday?
A3	Did you have at least two (2) consecutive hours of headache yesterday?
A4	What was the greatest severity that your headache reached at anytime yesterday?
A5	How many total hours did you have a headache of any severity yesterday?
A6	How many total hours of moderate or severe headache did you have yesterday?
B1	Was it worse on one side of the head than on the other, and/or limited to one side of the head?
B2	Was it pounding, pulsating, or throbbing?
B3	Was it made worse by routine activities such as walking or climbing stairs?
B4	Did you have nausea, or get sick to your stomach?
B5	Did light bother you more than when you didn't have a headache (did you experience photophobia)?
B6	Did sounds bother you more than when you didn't have a headache (did you experience phonophobia)?
B7	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" around the time of your headache? (This is different from "light bothers you".)
B8	Did you have feelings such as numbness or tingling in any part of your body or face around the time of your headache?

B9	Did you experience something like seeing spots, stars, lines, flashing lights, zigzag lines, or "heat waves" similar to those you may have seen when you have a headache? (This is different from "light bothers you")
B10	Did you have feelings such as numbness or tingling in any part of your body or face, similar to what you may have felt when you have a headache?
C1	What would better describe in general, how did you feel yesterday?
D1	Did you take any medications yesterday for your headache/migraine?
D2	Did you use any over the counter medications in an effort to get relief from your headache/migraine?
D3	Did you use Ergot/Triptan in an effort to get relief from your headache/migraine?
D4	Did you use any prescription medications other than Ergot/Triptan in an effort to get relief from your headache/migraine?

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CT-8.2.2.2	Potentially Drug-related TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.2.2.3	Potentially Drug-related TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.2.3.1	TEAEs Related to AI Device by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.2.3.2	TEAEs Related to AI Device by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.2.3.3	TEAEs Related to AI Device by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.2.4.1	TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.2.4.2	TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.2.4.3	TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Self-Administration at Home (SS)

CT-8.3.1.1	TEAEs by Severity by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.3.1.2	TEAEs by Severity by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.3.1.3	TEAEs by Severity by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.3.2.1	Potentially Drug-related TEAEs by Severity by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.3.2.2	Potentially Drug-related TEAEs by Severity by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.3.2.3	Potentially Drug-related TEAEs by Severity by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.3.3.1	TEAEs Related to AI Device by Severity by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.3.3.2	TEAEs Related to AI Device by Severity by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.3.3.3	TEAEs Related to AI Device by Severity by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.3.4.1	TEAEs Related to Subject Manipulation by Severity by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.3.4.2	TEAEs Related to Subject Manipulation by Severity by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.3.4.3	TEAEs Related to Subject Manipulation by Severity by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.4.1.1	TEAEs With an Outcome of Death by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.4.1.2	TEAEs With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.4.1.3	TEAEs With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Home (SS)

CT-8.4.2.1	Potentially Drug-related TEAEs With an Outcome of Death by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.4.2.2	Potentially Drug-related TEAEs With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.4.2.3	Potentially Drug-related TEAEs With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.4.3.1	TEAEs Related to AI Device With an Outcome of Death by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.4.3.2	TEAEs Related to AI Device With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.4.3.3	TEAEs Related to AI Device With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.4.4.1	TEAEs Related to Subject Manipulation With an Outcome of Death by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.4.4.2	TEAEs Related to Subject Manipulation With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.4.4.3	TEAEs Related to Subject Manipulation With an Outcome of Death by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.5.1.1	Serious TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.5.1.2	Serious TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.5.1.3	Serious TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.5.2.1	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)

CT-8.5.2.2	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.5.2.3	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.5.3.1	Serious TEAEs Related to AI Device by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.5.3.2	Serious TEAEs Related to AI Device by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.5.3.3	Serious TEAEs Related to AI Device by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.5.4.1	Serious TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.5.4.2	Serious TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.5.4.3	Serious TEAEs Related to Subject Manipulation by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.6.1.1	TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.6.1.2	TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.6.1.3	TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.6.2.1	Potentially Drug-related TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.6.2.2	Potentially Drug-related TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.6.2.3	Potentially Drug-related TEAEs Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Home (SS)

CT-8.6.3.1	TEAEs Related to AI Device Leading to Discontinuation of the IMP by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.6.3.2	TEAEs Related to AI Device Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.6.3.3	TEAEs Related to AI Device Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.6.4.1	TEAEs Related to Subject Manipulation Leading to Discontinuation of the IMP by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.6.4.2	TEAEs Related to Subject Manipulation Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.6.4.3	TEAEs Related to Subject Manipulation Leading to Discontinuation of the IMP by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.7.1.1	TEAEs Reported in at Least 2% of Subjects for Overall Treatment Period (SS)
CT-8.7.1.2	TEAEs Reported in at Least 2% of Subjects for Self-Administration at Trial Site (SS)
CT-8.7.1.3	TEAEs Reported in at Least 2% of Subjects for Self-Administration at Home (SS)
CT-8.7.2.1	Potentially Drug-related TEAEs Reported in at Least 2% of Subjects for Overall Treatment Period (SS)
CT-8.7.2.2	Potentially Drug-related TEAEs Reported in at Least 2% of Subjects for Self-Administration at Trial Site (SS)
CT-8.7.2.3	Potentially Drug-related TEAEs Reported in at Least 2% of Subjects for Self-Administration at Home (SS)
CT-8.7.3.1	TEAEs Related to AI Device Reported in at Least 2% of Subjects for Overall Treatment Period (SS)

CT-8.7.3.2	TEAEs Related to AI Device Reported in at Least 2% of Subjects for Self-Administration at Trial Site (SS)
CT-8.7.3.3	TEAEs Related to AI Device Reported in at Least 2% of Subjects for Self-Administration at Home (SS)
CT-8.7.4.1	TEAEs Related to Subject Manipulation Reported in at Least 2% of Subjects for Overall Treatment Period (SS)
CT-8.7.4.2	TEAEs Related to Subject Manipulation Reported in at Least 2% of Subjects for Self-Administration at Trial Site (SS)
CT-8.7.4.3	TEAEs Related to Subject Manipulation Reported in at Least 2% of Subjects for Self-Administration at Home (SS)
CT-8.8.1.1	Injection Site Reaction TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.8.1.2	Injection Site Reaction TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.1.3	Injection Site Reaction TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.8.2.1	Ophthalmic TEAEs of at Least Moderate Severity by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.8.2.2	Ophthalmic TEAEs of at Least Moderate Severity by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.2.3	Ophthalmic TEAEs of at Least Moderate Severity by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.8.3.1	Drug-related Hepatic TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.8.3.2	Drug-related Hepatic TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.3.3	Drug-related Hepatic TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.8.4.1	Anaphylaxis and Severe Hypersensitivity Reaction TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)

CT-8.8.4.2	Anaphylaxis and Severe Hypersensitivity Reaction TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.4.3	Anaphylaxis and Severe Hypersensitivity Reaction TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.8.5.1	Cardiovascular-related TEAEs by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.8.5.2	Cardiovascular-related TEAEs by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.5.3	Cardiovascular-related TEAEs by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-8.8.6.1	Non-Serious TEAEs Greater Than or Equal to 5% by MedDRA SOC and PT for Overall Treatment Period (SS)
CT-8.8.6.2	Non-Serious TEAEs Greater Than or Equal to 5% by MedDRA SOC and PT for Self-Administration at Trial Site (SS)
CT-8.8.6.3	Non-Serious TEAEs Greater Than or Equal to 5% by MedDRA SOC and PT for Self-Administration at Home (SS)
CT-9.1	Listing of Serious Adverse Events (SS)
CT-9.2	Listing of Adverse Events Leading to Discontinuation of the IMP (SS)
CT-9.3	Listing of Deaths (SS)
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CT-9.5	Listing of Ophthalmic Adverse Events of at Least Moderate Severity (SS)
CT-9.6	Listing of Drug-related Hepatic Adverse Events (SS)
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CT-9.8	Listing of Cardiovascular-related Adverse Events (SS)
CT-10.1.1	Descriptive Statistics for Laboratory Values (Serum Chemistry) (SS)
CT-10.1.2	Descriptive Statistics for Laboratory Values (Hematology) (SS)

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CT-10.2.1	Incidences of PCS Abnormalities in Laboratory Tests (Serum Chemistry) (SS)
CT-10.2.2	Incidences of PCS Abnormalities in Laboratory Tests (Hematology and Coagulation) (SS)
CT-10.2.3	Incidences of PCS Abnormalities in Laboratory Tests (Urinalysis) (SS)
CT-10.3.1	Listing of PCS Abnormalities in Serum Chemistry Laboratory Tests (SS)
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CT-10.4.1	Shift Table of Laboratory Values (Serum Chemistry) (SS)
CT-10.4.2	Shift Table of Laboratory Values (Hematology) (SS)
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CT-11.1	Descriptive Statistics for Vital Sign and Weight Values (SS)
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CT-12.2	Shift Table of ECG Findings (Investigators ECG Interpretation) (SS)
CT-12.3	Incidence of Categorical Changes in ECG Parameters (SS)
CT-12.4	Listing of Categorical Changes in Electrocardiogram Evaluations (SS)
CT-13.1	Injection Site Assessments - Injection-site Pain (SS)

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Appendix 5 List of Subject Data Listings

PDATA-1	Subject Disposition (Enrolled Subjects)
PDATA-2	Analysis Population Flag (Enrolled Subjects)
PDEV-1	Major Protocol Deviations (Enrolled Subjects)
DEMOG-1	Demographics (Enrolled Subjects)
DEMOG-2	Initial Migraine Diagnosis Date (Enrolled Subjects)
DEMOG-3	Childbearing Potential (Females Only) (Enrolled Subjects)
PDATA-3	Medical History (Enrolled Subjects)
PDATA-4	Complications (Enrolled Subjects)
PDATA-5	Prior and Concomitant Medications and Therapy (Enrolled Subjects)
SMED-1	Study Drug Administration (Enrolled Subjects)
SMED-2	Extent of Exposure (Enrolled Subjects)
SMED-3	Judgment on Self-administration (Enrolled Subjects)
SMED-4	Adherence to Self-administration Procedure (Enrolled Subjects)
SMED-5	Problems With AI Device (Enrolled Subjects)
PDATA-6	Vital Signs Values (Enrolled Subjects)
PDATA-7.1	Electrocardiogram Measurement (Enrolled Subjects)
PDATA-7.2	Electrocardiogram Interpretation (Enrolled Subjects)
PDATA-7.3	Electrocardiogram Findings (Enrolled Subjects)
PDATA-7.4	Electrocardiogram Technical (Enrolled Subjects)
PDATA-8	Physical Examination Findings (Enrolled Subjects)
PDATA-9	Columbia-Suicide Severity Rating Scale Assessment (Enrolled Subjects)
PDATA-10	Injection Site Assessment (Enrolled Subjects)
PDATA-11	Screen Failures (Screen Failure)

PDATA-12	Subjects Who Did Not Meet Inclusion Criteria or Meet Exclusion Criteria (Screen Failure)
PDATA-13	Pharmacokinetic Blood Draw Date and Times (Enrolled Subjects)
PDATA-14	Anti-drug Antibodies Blood Draw Date and Times (Enrolled Subjects)
PDATA-15	Subjects Who Did Not Meet Inclusion Criteria or Meet Exclusion Criteria (Enrolled Subjects)
PDATA-16	Information on Subjects Lost to Follow-up (Enrolled Subjects)
EFF-1	Electronic Headache Diary Questionnaire - Questions List
EFF-2	Electronic Headache Diary Questionnaire - Results (Enrolled Subjects)
EFF-3	Electronic Headache Diary Questionnaire - Derived (Enrolled Subjects)
AE-1	Treatment-Emergent Adverse Events (Enrolled Subjects)
AE-2	Prior to Treatment Adverse Events (Enrolled Subjects)
LAB-1	Serum Chemistry Laboratory Tests Results (Enrolled Subjects)
LAB-2	Hematology Laboratory Tests Results (Enrolled Subjects)
LAB-3	Coagulation Laboratory Tests Results (Enrolled Subjects)
LAB-4	Urinalysis Laboratory Tests Results (Enrolled Subjects)
LAB-5	Pregnancy Test Results (Females Only) (Enrolled Subjects)