STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Episodic Migraine

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
TEV-48125

Protocol No. 406-102-00002

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Episodic Migraine

Statistical Analysis Plan

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
CM	Chronic migraine
CMH	Cochran-Mantel-Haenszel
ECG	Electrocardiogram
EM	Episodic migraine
EOT	End of Treatment
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
ES	Enrolled Set
FAS	Full Analysis Set
IGS	Immunogenicity Analysis set
IMP	Investigational medicinal product
IRT	Interactive response technology
LS mean	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
MMRM	Mixed-effects model for repeated measures
MSQOL	Migraine-Specific Quality of Life
PCS	Potentially Clinically Significant
PGIC	Patient Global Impression of Change
PHQ-2	2-Item Patient Health Questionnaire
PHQ-9	9-Item Patient Health Questionnaire
PKS	Pharmacokinetic Analysis set
PT	Preferred Term
RS	Randomized Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SS	Safety Set
TEAE	Treatment-emergent adverse event
WPAI	Work Productivity and Activity Impairment

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 406-102-00002. Analysis of immunogenicity is described in the bioanalytical protocol. All amendments to the protocol are taken into consideration in developing the SAP.

2 Trial Objectives

To evaluate the efficacy and safety of subcutaneous (SC) administration of TEV-48125 (monthly TEV-48125 225 mg and TEV-48125 675 mg once over a period of 3 months) compared with placebo for preventive treatment in episodic migraine (EM) patients.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in EM patients. The schematic of the trial design is shown in Figure 3.1-1.

The trial consists of a 4-week screening period and a 12-week double-blind treatment period.

After obtaining written informed consent from patients, the investigator will screen them for eligibility (Visit [V] 1/Screening). Subjects who have been diagnosed with EM, and who meet all the inclusion criteria and do not fall under any of the exclusion criteria will be randomized in a 1:1:1 ratio to one of the following 3 treatment groups (V2/Baseline). The investigational medicinal product (IMP) will be administered at V2/Baseline, V3/Month 1, and V4/Month 2 as specified in the protocol Section 3.2, Trial Treatments. Subjects will also visit the trial site at 3 to 10 days and at 14 to 21 days (twice) after one of IMP administrations at either V2/Baseline, V3/Month 1, or V4/Month 2 for pharmacokinetic assessment. Subjects will also return to the trial site (V5/End of treatment) for the final assessment at 12 weeks after the first IMP administration. Subjects who are withdrawn from the trial will undergo a withdrawal assessment.

The trial includes the following treatment groups.

- TEV-48125 225/225/225 mg group
- TEV-48125 675 mg/placebo/placebo group

- Placebo group

The period of trial participation for each subject is defined as the period from the day that informed consent is obtained from the patient until the day of trial completion.

Definition of the end of trial date for individual subject:

The end of trial date for individual subject is defined as the date of V5/End of treatment for the final assessment/observation or the date of trial withdrawal. The date of trial withdrawal is defined as the date of withdrawal assessment, the date of the final assessment/observation in the double-blind treatment period, or the date of withdrawal decision, whichever comes later. For subjects who are lost to follow up, the end of trial date for individual subject is defined as the date of their last visit/contact or the date of the last attempt to contact them.

Following the end of treatment visit (V5/End of treatment), subjects will be offered the opportunity to enter a long-term trial for the purpose of evaluating antidrug antibody (ADA) at 225 days (approximate equivalent of 5 half-lives) after the final dose of IMP (V4/Month 2) in this trial.

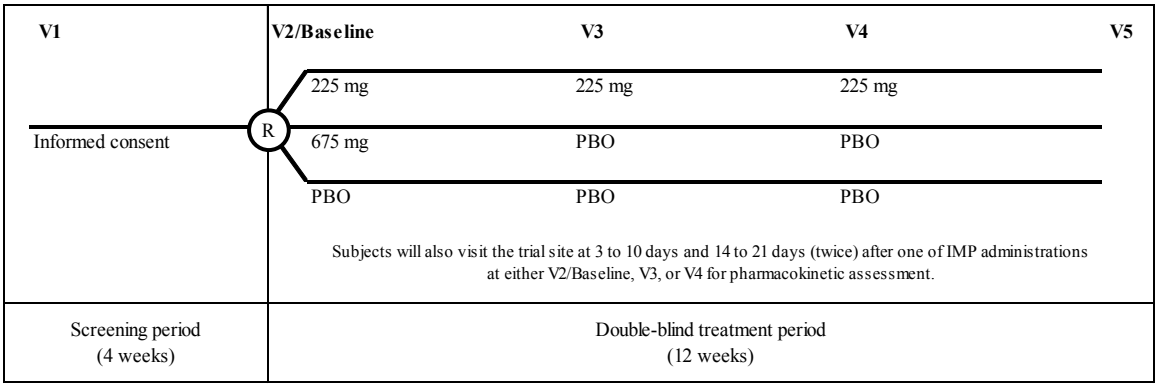

Figure 3.1-1 Trial Design Schematic

PBO = placebo; R = randomization.

As described in the protocol Section 1.6, Suspension and Resumption of the Trial, the trial was previously suspended due to an error in the interactive response technology (IRT) system. The 96 subjects who were randomized prior to trial suspension are defined as Cohort 1 (subjects in the 225/225/225 mg group were administered an initial dose of 675 mg, which was higher than that planned in the protocol), and the subjects enrolled after trial resumption are defined as Cohort 2.

3.2 Trial Treatments

In the trial, TEV-48125 or placebo will be subcutaneously administered once monthly for 3 months for a total of 3 doses. Monthly dosing refers to dosing every 4 weeks (acceptable window: ± 3 days). Subjects who visit the trial site earlier than the acceptable window will not receive the IMP and will be requested to return to the trial site within the acceptable window. The IMP will be administered by trial personnel responsible for administration of injections.

The dosing regimens for treatment groups are shown below.

- TEV-48125 225/225/225 mg group:
  Subjects will receive 225 mg of TEV-48125 as a single active injection (225 mg/1.5 mL) and placebo as two 1.5-mL injections at V2/Baseline and 225 mg of TEV-48125 as a single active injection (225 mg/1.5 mL) at V3/Month 1 and V4/Month 2.
- TEV-48125 675 mg/placebo/placebo group:
  Subjects will receive 675 mg of TEV-48125 as 3 active injections (225 mg/1.5 mL) at V2/Baseline and placebo as a single 1.5-mL injection at V3/Month 1 and V4/Month 2.
- Placebo group:
  Subjects will receive three 1.5-mL placebo injections at V2/Baseline and a single 1.5-mL placebo injection at V3/Month 1 and V4/Month 2.

At the time of each visit, the IRT will be queried and trial personnel will retrieve and administer a 1.5-mL volume from each syringe contained in the appropriately numbered kit(s).

Recommended SC injection sites follow the National Institutes of Health clinical center patient education materials: Giving a subcutaneous injection.[1] The suggested sites of injection are the outside of upper arms, back of upper arms, abdomen, or front of thighs. At each visit and when 3 injections are administered at a visit, each of the injections should be given in a different location (eg, not in precisely the same place). Trial personnel responsible for administration of injections should inspect previous injection sites to ensure that they are free from bruising and tenderness and that proper rotation of sites is performed.

IMP should be removed from the refrigerator and allowed to equilibrate at room temperature for 45 to 60 minutes before IMP administration.

The total number of SC injections and their locations will be recorded for each dosing visit (V2/Baseline, V3/Month 1, and V4/Month 2).

3.3 Trial Population

3.3.1 Subject Groups

The 96 subjects who were randomized prior to trial suspension due to an error in the IRT system are defined as Cohort 1. The subjects enrolled after trial resumption are defined as Cohort 2.

3.3.2 Number of Subjects in Cohort 2

A total of 330 male or female (110 per group, a total of 3 groups) with EM aged 18 to 70 years, inclusive, will be enrolled in the trial (Cohort 2). The plan is to enroll at least approximately half of the subjects in Japan. The enrollment procedure will be continued until the number of enrolled subjects reaches 330 in Cohort 2.

Continued concomitant use of some preventive migraine medications (Table 4.1.2-1 in the protocol) may be permitted, so long as a stable dose and regimen have been maintained for at least 2 consecutive months prior to informed consent, in which case the subject will be allowed to continue using no more than 1 preventive medication. However, the total number of subjects receiving concomitant preventive medication during the trial will not exceed 30% of the total sample size of the trial.

4 Sample Size (Cohort 2)

In a phase 2b trial (Trial LBR-101-022) in EM patients, concerning the mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP, the difference between the TEV-48125 225/225/225 mg group and the placebo group was 2.7 days and the standard deviation was 4.1 days. Conservatively, a treatment difference between each TEV-48125 group and the placebo group and its standard deviation in the current trial are assumed to be 1.8 days and 4.1 days, respectively, and a sample size of 110 subjects per group gives more than 90% power for the trial to succeed at a significance level of 0.05 (two-sided).

Based on the above, the target sample size was determined to be 110 subjects per group and 330 subjects in total for Cohort 2.

5 Statistical Analysis Datasets

5.1 Analysis Sets

- Enrolled set (ES):
  Subjects from whom informed consent has been obtained

(1) Cohort 1

- Randomized set 1 (RS 1):
  Randomized subjects in the ES who are in Cohort 1
- Safety set 1 (SS 1):
  Subjects in the RS1 who receive the IMP at least once
- Pharmacokinetic Analysis set in Cohort 1 (PKS 1):
  The PKS 1 will include all subjects in whom at least 1 dose of TEV-48125 is administered, and date and time of blood sampling for plasma drug concentration is recorded for at least 1 time point after TEV-48125 dosing.
- Immunogenicity Analysis set in Cohort 1 (IGS 1):
  The IGS 1 will include all subjects in whom at least 1 dose of TEV-48125 is administered, and date and time of blood sampling for serum ADA assessment is recorded for at least 1 time point after TEV-48125 dosing.

(2) Cohort 2

- RS 2 :
  Randomized subjects in the ES who are in Cohort 2
- SS 2:
  Subjects in the RS 2 who receive the IMP at least once
- Full Analysis set (FAS):
  Subjects in the SS 2 who have at least 10 days of baseline and post baseline efficacy assessment data on monthly average number of migraine days
- PKS 2:
  The PKS 2 will include all subjects in whom at least 1 dose of TEV-48125 is administered, and date and time of blood sampling for plasma drug concentration is recorded for at least 1 time point after TEV-48125 dosing.
- IGS 2:
  The IGS 2 will include all subjects in whom at least 1 dose of TEV-48125 is administered, and date and time of blood sampling for serum ADA assessment is recorded for at least 1 time point after TEV-48125 dosing.

For all analysis sets except for ES, treatment will be assigned based on the treatment to which subjects are randomized regardless of which treatment they actually received.

5.2 Handling of Missing Data

Information on missing data is handled within the analysis sections.

6 Primary and Secondary Endpoints:

6.1 Primary Endpoint

- Mean change from baseline in the monthly* average number of migraine days during the 12-week period after the first dose of IMP

  * "the monthly" is defined as "28-day" in this trial.

6.2 Secondary Endpoints

- Proportion of subjects reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP
- Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
- Mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications
- Mean change from baseline in disability score, as measured by the Migraine Disability Assessment (MIDAS) questionnaire, at 4 weeks after the final (third) dose of IMP

7 Disposition and Demographic Analysis

Descriptive statistics include number of subject (n), mean, standard deviation (SD), median, minimum, and maximum.

7.1 Subject Disposition

Data will be summarized for the overall population and by country.

The number of subjects from whom informed consent has been obtained, screen failure subjects and randomized subjects will be provided for the ES.

The number and percentage of subjects in whom IMP is administrated, in whom IMP is not administrated, who complete the trial, and who are withdrawn from the trial will be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2. The primary reason for discontinuation will also be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2.

The number and percentage of subjects who are included in the SS 1, PKS 1, IGS 1, and who are excluded from the SS 1, PKS 1, and IGS 1 will be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1.

The number and percentage of subjects who are included in the SS 2, FAS, PKS 2, IGS 2, and who are excluded from the SS 2, FAS, PKS 2, IGS 2 will be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 2.

7.2 Demographic and Baseline Characteristics

Data will be summarized for the overall population and by country in each cohort.

The following demographic and baseline characteristics will be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2. Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using number and percentage of subjects.

- Age ([≤45, ≥46 to ≤64, ≥65], [≤45, >45]), sex
- Country, ethnicity, detailed ethnicity (Japanese, Korean), race
- Weight, 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 Ver. 22.0) preferred term (PT). The number and percentage of subjects with medical history and complications will be summarized by SOC and PT for the RS 1 and RS 2. Subjects are counted only once in each SOC and only once in each PT.

7.3 Baseline Disease Evaluation

Data will be summarized for the overall population and by country.

The following baseline disease evaluation will be summarized by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2. Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using number and percentage of subjects.

- Number of headache days of any duration and any severity
- Number of migraine days
- Number of headache days of at least moderate severity
- Use of any acute headache medications (yes/no)
- Use of migraine-specific acute headache medications (triptans and ergot compounds) (yes/no)

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 Technical Computational Details for Primary Analysis 8.1.4) using the electronic headache diary data collected through the corresponding headache diary questions.

7.4 Treatment Compliance

Information for administration of IMP is described in Section 9.1.

7.5 Prior and Concomitant Medications

Data will be summarized for the overall population and by country, by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2.

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 Enhanced B2 March 2017). 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 4.1.2-1 in the protocol) used at baseline will also be summarized.

7.6 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 by treatment group, for all TEV-48125-treated subjects, and overall for the RS 1 and RS 2.

8 Efficacy Analysis

The FAS will be used for all efficacy analyses. Summaries will be presented by treatment group, unless otherwise noted. Descriptive statistics for all efficacy data will be presented by month (or week) and overall for the 12-week period. Descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

8.1 Primary Endpoint

8.1.1 Primary Analysis

The primary efficacy endpoint is mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP.

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model. The model will include treatment, sex, country, and baseline preventive medication use as fixed effects and baseline number of migraine days and years since onset of migraines as covariates. Two-sided 95% confidence intervals and p-values will be constructed for the least squares (LS) mean differences between each TEV-48125 group and the placebo group.

The following sample SAS code pertains to the primary analysis.

```
proc mixed;
   class TREATMENT SEX PRVMBASE CONTRY;
   model CHG = BASE TTMIG PRVMBASE SEX TREATMENT CONTRY /s;
   lsmeans TREATMENT /pdiff cl alpha =0.05;
   ods output diffs = DIFFS lsmeans = LSMEANS;
run;
*PRVMBASE: Baseline preventive medication use
*TTMIG        : Years since onset of migraines
```

Multiplicity problems will be avoided using a closed testing procedure. If superiority of the TEV-48125 225/225/225 mg group to the placebo group is confirmed at a two-sided

significance level of 0.05, then the TEV-48125 675 mg/placebo/placebo group vs the placebo group will be tested at a two-sided significance level of 0.05.

8.1.2 Sensitivity Analyses

8.1.2.1 Wilcoxon Rank-sum Test

The primary endpoint will be also analyzed using Wilcoxon rank-sum test to compare each TEV-48125 group vs the placebo group.

8.1.2.2 Analysis With Multiple Imputation Method

Regarding the primary endpoint, when the monthly average number of migraine days during the 12-week period after the first dose of IMP is not missing, but any of the monthly number of migraine days during the 4-week period after each dose of IMP (ie, Month 1, Month 2, and Month 3) is missing, the multiple imputation (MI) method will be applied to impute the missing data for Month 1, Month 2, or Month 3 and the primary endpoint will be calculated as the average of Month 1, Month 2, and Month 3. The data will be processed by the following steps.

- If a subject has partial electronic headache diary data for a month, ie, <10 days of data, a value for that month will be considered missing before the MI procedure.
- Subjects in each TEV-48125 group who are withdrawn early for reasons of adverse events (AEs) or lack of efficacy will be assigned to the placebo group and their missing values will be imputed using data from the placebo-treated subjects.
- The SAS MI procedure will be run to create 100 complete datasets.
- Within each imputed data set, for a subject who has partial, eg, X days (X <10) , electronic headache diary data for a month, the monthly value will be replaced by $\sum(observed\ migraine\ days) + (28 - X) * imputed\ value/28$
- The monthly average number of migraine days during the 12-week period after the first dose of IMP will be the average of the Month 1, Month 2, and Month 3 values.

Each dataset including the monthly average during the 12-week period will be analyzed using the same ANCOVA model as described in Section 8.1.1. The LS means and standard errors (SE) from each analysis will be output to a SAS data set. The SAS MIANALYZE procedure will be used to generate the final LS means (± SE) for the treatment groups and the treatment differences (each TEV-48125 group − placebo group) as well as the p-values associated with treatment differences. The 95% confidence intervals for the treatment differences will also be constructed.

8.1.3 Supplementary Analyses

A mixed-effects model for repeated measures (MMRM) analysis will be used to estimate the mean change from baseline in the monthly number of migraine days for the overall 3-month treatment period and by each month to support the primary analysis.

The MMRM will include treatment, sex, country, baseline preventive migraine medication use, month and treatment-by-month interaction as fixed effects and baseline value and years since onset of migraines as covariates. The unstructured covariance structure will be used for repeated observations within a subject. Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The LS means for the treatment groups, LS means for the treatment differences (each TEV-48125 group − placebo group), and corresponding 95% confidence intervals and associated p-values will be calculated by month and for the overall treatment period.

The following SAS code pertains to the MMRM analysis.

```
proc mixed method = reml;
   class USUBJID MONTH TREATMENT SEX PRVMBASE CONTRY;
   model CHG = BASE TTMIG PRVMBASE SEX TREATMENT MONTH
      TREATMENT * MONTH CONTRY /s ddfm=kr;
   repeated MONTH /subject = USUBJID type = un r;
   lsmeans TREATMENT TREATMENT * MONTH / pdiff cl alpha = 0.05;
   ods output diffs = DIFFS lsmeans = LSMEANS;
run;
*PRVMBASE: Baseline preventive medication use
*TTMIG     : Years since onset of migraines
```

If any problems in convergence status arise in the estimation of variance components, heterogeneous Toeplitz, heterogeneous autoregressive of order 1, and heterogeneous compound symmetry, which are error variance-covariance structures, will be applied in that order, and the first structure that achieves convergence will be used. If anything other than an unstructured variance-covariance structure is selected, a sandwich estimator for standard errors will be used.

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

Mean change from baseline in the monthly number of migraine days during the 4-week period after each dose (ie, for Month 1, Month 2, and Month 3) will also be estimated and

compared by the same ANCOVA model as described in Section 8.1.1 and by Wilcoxon rank-sum test as described in Section 8.1.2.

8.1.4 Technical Computational Details for Primary Analysis

- Definition of migraine day

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

  – A calendar day (0000 to 2359) demonstrating at least 2 consecutive hours of headache meeting the criteria for migraine with or without aura

  – A calendar day (0000 to 2359) demonstrating 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 headache of any duration that was treated with migraine-specific medication (triptans and ergot compounds)

  The derivation logic is presented in Appendix 1.

- Variable definitions

  The change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP will be derived using the electronic headache diary data collected for the corresponding headache diary questions. 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 migraine days during the 12-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.

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

  The monthly number of migraine days during the 4-week period after each dose (ie, for Month 1, Month 2, and Month 3), will be derived and normalized to 28 days (see the following formula), where monthly data separated by each visit for IMP dosing will be used. 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.

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

8.2 Secondary Endpoint

8.2.1 Secondary Analysis

The secondary endpoints in this trial are as follows:

1) Proportion of subjects reaching at least 50% reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP
2) Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
3) Mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications
4) Mean change from baseline in disability score, as measured by the MIDAS questionnaire, at 4 weeks after the final (third) dose of IMP

For the endpoint 1), each TEV-48125 group and the placebo group will be compared using Cochran-Mantel-Haenszel (CMH) test stratified by baseline preventive medication use. The difference in the endpoint 1) between each TEV-48125 group and the placebo group and its two-sided 95% confidence interval (a Mantel-Haenszel estimator of the difference and its two-sided 95% confidence interval) will be computed. Additionally, two-sided 95% confidence interval for the endpoint 1) in each treatment group will also be calculated using Clopper-Pearson method. Furthermore, proportion of subjects reaching at least 50% reduction in the monthly number of migraine days during the 4-week period after each dose (ie, for Month 1, Month 2, and Month 3) will also be computed in the same manner. Missing data of evaluation will not be imputed.

The endpoints 2) and 3) will be analyzed using an ANCOVA model, Wilcoxon rank-sum test, and MMRM in the same manner as described in Section 8.1. The LS means ± SE of monthly change from baseline values estimated by the MMRM will also be plotted.

For the endpoint 4), the MIDAS total score will be used for disability score. The ANCOVA model and Wilcoxon rank-sum test will be performed as described in Section 8.1. Frequency distributions will also be provided by MIDAS grade for baseline and 4 weeks after the final (third) dose of IMP in each treatment group.

8.2.2 Technical Computational Details for Secondary Analysis

- Variable definitions
  - Electronic Headache Diary Data

The monthly average number of days for secondary endpoints (eg, migraine days, days with use of any acute headache medications, etc.) during the 12-week period after the first dose of IMP will be derived similar to the primary endpoint using the electronic headache diary data collected for the corresponding headache diary questions. The baseline value and monthly number of days for endpoints during the 4-week period after each dose (ie, for Month 1, Month 2, and Month 3) will be derived in the same manner (see Technical Computational Details for Primary Analysis 8.1.4).

– Migraine Disability Assessment (MIDAS)

The MIDAS total score and MIDAS grade will be derived based on attachment 2 in the protocol. Baseline will be the last value prior to the first dose of IMP. Post-baseline (4 weeks after the final [third] dose of IMP) will be the nominal visit.

8.3 Exploratory Endpoints

8.3.1 Number of Migraine Days

The exploratory endpoints for number of migraine days in this trial are as follows:

1) Mean change from baseline in the weekly number of migraine days during the 4-week period after the first dose of IMP
2) Proportion of subjects reaching at least 75% reduction and total (100%) reduction in the monthly average number of migraine days during the 12-week period after the first dose of IMP
3) Proportion of subjects reaching at least 50% reduction and at least 75% reduction in the number of migraine days during the 4-week period after the first dose of IMP for whom this level of effect is sustained throughout the 12-week period after the first dose of IMP
4) Mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP in subjects receiving concomitant preventive migraine medications

For the endpoint 1), similar to the supplementary analysis for the primary endpoint described in Section 8.1.3, an ANCOVA model, Wilcoxon rank-sum test, and MMRM will be used to estimate the mean change from baseline by week (ie, for Week 1, Week 2, Week 3 and Week 4) after the first dose of IMP.

The endpoint 2) will be analyzed using CMH method as described in Section 8.2.1 “endpoint 1)”.

The endpoint 3) will be analyzed using CMH test stratified by baseline preventive migraine medication use similar to “endpoint 1)” in Section 8.2.1. If the subject shows 50% reduction or more at Month 1, Month 2, and also Month3, the level of effect is

considered to be sustained throughout the 12-week period after the first dose of IMP for this subject. A subjects with a missing will be treated as a non-responder. Similar definition will be applied to calculate the proportion of sustained responders reaching at least 75% reduction.

The endpoint 4) will be analyzed using an ANCOVA model, Wilcoxon rank-sum test, and MMRM in the same manner as described in Section 8.1.

8.3.2 Number of Headache Days of at Least Moderate Severity

The exploratory endpoints for number of headache days of at least moderate severity in this trial are as follows:

1) Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP
2) Mean change from baseline in the weekly number of headache days of at least moderate severity during the 4-week period after the first dose of IMP
3) Proportion of subjects reaching at least 50% reduction, at least 75% reduction, and total (100%) reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP
4) Proportion of subjects reaching at least 50% reduction and at least 75% reduction in the number of headache days of at least moderate severity during the 4-week period after the first dose of IMP for whom this level of effect is sustained throughout the 12-week period after the first dose of IMP
5) Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications
6) Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP in subjects receiving concomitant preventive migraine medications

The endpoint 1) will be analyzed using an ANCOVA model, Wilcoxon rank-sum test, and MMRM in the same manner as described in Section 8.1. The LS means ± SE of monthly change from baseline values estimated by the MMRM will also be plotted.

The endpoint 2) will be analyzed in the same manner as “endpoint 1)” in Section 8.3.1.

The endpoint 3) will be analyzed in the same manner as “endpoint 1)” in Section 8.2.1.

The endpoint 4) will be analyzed in the same manner as “endpoint 3)” in Section 8.3.1.

The endpoints 5) and 6) will be analyzed in the same manner as “endpoint 4)” in Section 8.3.1.

8.3.3 Other Headache-related Endpoints

The other exploratory headache-related endpoints in this trial are as follows:

1) Mean change from baseline in the monthly average number of headache days of any severity during the 12-week period after the first dose of IMP
2) Mean change from baseline in the monthly average number of headache hours of any severity during the 12-week period after the first dose of IMP
3) Mean change from baseline in the monthly average number of headache hours of at least moderate severity during the 12-week period after the first dose of IMP
4) Mean change from baseline in the monthly average number of days with use of migraine-specific acute headache medications (triptans and ergot compounds) during the 12-week period after the first dose of IMP in subjects who used migraine-specific acute headache medications (triptans and ergot compounds) at baseline
5) Mean change from baseline in the monthly average number of days with nausea or vomiting during the 12-week period after the first dose of IMP
6) Mean change from baseline in the monthly average number of days with photophobia and phonophobia during the 12-week period after the first dose of IMP

These endpoints will be analyzed in the same manner as Section 8.1.

8.3.4 Other Efficacy Endpoints

The other exploratory efficacy endpoints collected using Electronic Patient-Reported Outcomes (ePRO) in this trial are as follows:

1) Mean change from baseline in quality of life, as measured by the Migraine-Specific Quality of Life Questionnaire (MSQOL) questionnaire, at each visit after IMP administration.
2) The health status quality of life, as measured by the EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire at 4 weeks after the final (third) dose of IMP
3) Mean change from baseline in subject depression status, as measured by the Two-Item Patient Health Questionnaire/Nine-Item Patient Health Questionnaire (PHQ-2/ PHQ-9) at 4 weeks after the final (third) dose of IMP
4) Mean change from baseline in subject work productivity and activity impairment, as measured by the Work Productivity and Activity Impairment (WPAI) at 4 weeks after the final (third) dose of IMP
5) Assessment of patient satisfaction, as measured by the Patient Global Impression of Change (PGIC) scale, at each visit after IMP administration.

For the endpoint 1), the transformed scores for the three domains (ie, Role Function-Restrictive, Role Function-Preventive, and Emotional Function) of MSQOL will be derived for baseline, V3/Month 1, V4/Month 2, and V5/End of treatment (Month 3). The scoring instructions are presented in Appendix 2. In each domain, transformed scores will be analyzed in the same manner as Section 8.1. Baseline will be the last value prior to the first dose of IMP. Post-baseline (V3/Month 1, V4/Month 2, and V5/End of treatment [Month 3]) will be the nominal visits.

For the endpoint 2), for each domain (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), frequency distributions will be provided by scale of 1 to 5 where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems for baseline and 4 weeks after the final (third) dose of IMP in each treatment group. The ANCOVA model and Wilcoxon rank-sum, test which are described in Section 8.1, will be performed for the visual analog scale. Baseline will be the last value prior to the first dose of IMP. Post-baseline (4 weeks after the final [third] dose of IMP) will be the nominal visit (V5/End of treatment [Month 3]).

For the endpoint 3), the total score will be analyzed using the ANCOVA model and Wilcoxon rank-sum test as described in Section 8.1. Baseline will be the last value prior to the first dose of IMP. Post-baseline (4 weeks after the final [third] dose of IMP) will be the nominal visit (V5/End of treatment [Month 3]).

For the endpoint 4), the following scores (in percentages) will be analyzed using the ANCOVA model and Wilcoxon rank-sum test which are described in Section 8.1. Baseline will be the last value prior to the first dose of IMP. Post-baseline (4 weeks after the final [third] dose of IMP) will be the nominal visit (V5/End of treatment [Month 3]). The scores (in percentages) will be derived based on the WPAI questionnaire as follows:

- Percent work item missed due to health: $\frac{Q2}{Q2+Q4}\times 100$
- Percent impairment while working due to health: $\frac{Q5}{10}\times 100$
- Percent overall work impairment due to health: $\left\{\frac{Q2}{Q2+Q4}+\left[1-\left(\frac{Q2}{Q2+Q4}\right)\times\frac{Q5}{10}\right]\right\}\times 100$
- Percent activity impairment due to health: $\frac{Q6}{10}\times 100$

For the endpoint 5), the number and percentage of PGIC responders (subjects whose PGIC score were 5 to 7) will be derived for V3/Month 1, V4/Month 2, and V5/End of treatment (Month 3). The percentage of PGIC responders will be analyzed by CMH test

stratified by baseline preventive migraine medication use as described in "endpoint 1)" in Section 8.2.1. Frequency distributions will also be provided by original response (scores: 1 to 7) at each visit in each treatment group.

8.3.5 Technical Computational Details for Exploratory Analysis

- Variable definitions
  - Electronic Headache Diary Data

  The weekly number of days for exploratory endpoints (eg, migraine days, headache days of at least moderate severity, etc.) during the 4-week period after the first dose of IMP will be derived using the electronic headache diary data collected for the corresponding headache diary questions. 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 7 days (see the following formula).

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ screening\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ screening\ period} \times 7$$

  The weekly number of days for exploratory endpoints will be calculated for the subject's first 28 calendar days of diary data after the first dose of IMP. Each week is defined as 7 calendar days, with Week 1 counted from the first dose date.

  If a subject has missing diary data in a week, the following method will be used to handle the missing data.

  - If the subject has ≥**3** days of electronic headache diary data for a week, the weekly number of days of exploratory endpoints will be prorated to 7 days for that week (see the following formula).

$$\frac{\sum Days\ of\ efficacy\ variable\ during\ the\ 7\ days\ period}{\sum Days\ with\ assessments\ recorded\ in\ the\ eDiary\ for\ the\ 7\ days\ period} \times 7$$

  - If the subject has <**3** days of electronic headache diary data for a week, the weekly number of days of efficacy variables will be considered as missing for that week.

  The monthly average number of days/hours for exploratory endpoints (eg, headache hours of any severity, headache hours of at least moderate severity, days with use of migraine-specific acute headache medications [triptans and ergot compounds], days with nausea or vomiting, days with photophobia and phonophobia, etc.) during the 12-week period after the first dose of IMP will be derived similar to the primary endpoint using the electronic headache diary data collected for the corresponding headache diary questions. The baseline value and monthly number of days/hours for endpoints during the 4-week period after each dose (ie, for Month 1, Month 2, and Month 3) will be derived in the same manner (see Technical Computational Details for Primary Analysis 8.1.4). In the case of hours, the numerator of formula will be hours instead of days.

- 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 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.

8.4 Subgroup Analyses

The following subgroups for the change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP and the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP will be analyzed in the same manner as Section 8.1.

- Country
- Age (≤45, >45)
- Sex

9 Safety Analyses

Safety analysis will be performed using both the SS 1 and the SS 2 as the analysis sets.

Summaries will be presented by treatment group and all TEV-48125 groups unless specified otherwise. Descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

9.1 Extent of Exposure

Data will be summarized for overall population and by country. Duration of treatment (days treated) is the number of days on treatment based on the first dose of IMP day and end of treatment (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, 2 doses, and 3 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, ≥2 months, ≥3 months). One month will be defined as 28 days. The total exposure of IMP allocated at in each visit (V2/Baseline, V3/Month 1, and V4/Month 2) 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:

- 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 in any treatment group

The above summaries will also be prepared for TEAEs potentially drug related, and for the overall population and by country. In addition, TEAEs will be summarized by age (<65, ≥65), sex and use of preventive migraine medication at baseline (yes, no).

- 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 in any treatment group

9.3 Clinical Laboratory Data

Descriptive statistics will be calculated for clinical laboratory data and changes from baseline at each time point (V3/Month 1, V4/Month 2, V5/End of treatment [Month 3], 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 3.

Shift tables (except qualitative urinalysis) will be created for baseline and post-baseline at each time point values classified into normal, high, or low based on the reference range.

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

9.4 Vital Sign and Weight Data

Descriptive statistics will be calculated for vital sign and weight measurements and changes from baseline at each time point (V3/Month 1, V4/Month 2, V5/End of treatment [Month 3], 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. Listing of subjects with PCS values will be prepared. The criteria are presented in Appendix 4.

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

9.5 Physical Examination Data

A list will be prepared for subjects with physical examination.

9.6 Electrocardiogram Data

Descriptive statistics will be calculated for electrocardiogram (ECG) measurements and changes from baseline at each time point (V5/End of treatment [Month 3], additional visits for pharmacokinetic [at 3 to 10 days and at 14 to 21 days postdose at V2/Baseline, V3/Month 1, and V4/Month 2], and at 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.

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

- Subject who attains a value >450 msec post-baseline*
- Subject who attains a value >480 msec post-baseline*
- Subject who attains a value >500 msec post-baseline*
- Increase in change from baseline value >30 msec at post-baseline*
- Increase in change from baseline value >60 msec at post-baseline*

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

The ECGs will be performed in triplicate. The average of the recorded measurements will be calculated for each visit. Baseline will be the last value prior to the first dose of IMP. Each visit for post-baseline will be the Nominal visits. Final evaluation will be the last observed all post-baseline data (including scheduled, unscheduled, additional visits for pharmacokinetic assessments, and withdrawal visits). Worst value will also be derived using all post-baseline data.

9.7 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/Baseline, V3/Month 1, and V4/Month 2) and time point (immediately postdose and 1 hour postdose).

9.8 Electronic Columbia-Suicide Severity Rating Scale

Frequency distributions will be provided by response (positive/negative) for baseline and post-baseline scores. Post-baseline will include all post-baseline data, and if at least one time point is positive, post-baseline will be positive. Subjects having positive findings will be listed.

10 Pharmacokinetic Analyses

10.1 Endpoint

Plasma TEV-48125 concentration

10.2 Dataset for Analysis

Pharmacokinetic analysis set (PKS 1 and PKS 2)

10.3 Handling of Data

- The plasma concentrations below lower limit of quantitation will be imputed to 0 (ng/mL). Lower limit of quantitation of TEV-48125 is 250 ng/mL.
- No imputation will be performed for missing data.

10.4 Statistical Analysis Method

Concerning 10.1 Endpoint, descriptive statistics will be calculated by treatment group at each blood sampling time point separately for PKS 1 and PKS 2. Descriptive statistics include the number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

11 Pharmacodynamic Analyses

There were no pharmacodynamic analyses in this trial.

12 Pharmacogenomic Analyses

There were no pharmacogenomic analyses in this trial.

13 Interim Analysis

None

14 Changes in the Planned Analyses

- Wilcoxon rank-sum test is conducted as the sensitivity analysis for normality assumption of the residuals in the primary efficacy analysis.
- The sensitivity analysis based on multiple imputation method is conducted to explore the impact of missing data in the primary efficacy analysis.
- MMRM analysis is added to estimate the mean change from baseline in the monthly number of headache days of at least moderate severity for the overall 3 months treatment period and by each month.
- The definitions of PKS 1, PKS 2, IGS 1 and IGS 2 were changed as described in Section 5.1. PKS 1, PKS 2, IGS 1 and IGS 2 will be determined based on the

TEV-48125 dosing and the presence of recording of the date and time of blood sampling, not based on the IMP dosing and the presence of the measured values as described in the protocol.

15 References

1 NIH clinical center patient education materials. Giving a subcutaneous injection. [Internet]. [cited 2017 Jul 3]. Available from: http://www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf.

Appendix 1 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 and 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	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

Appendix 2 Scoring Instructions for MSQ

The scoring of the MSQ is completed in 3 steps:

1. Recoding of MSQ items (final item value assignment)

   The precoded and final item values for each MSQ item response is shown in Table 15-1. All item values range from 1 to 6.

2. Computation of raw dimension scores

   Once a final item value has been assigned to each item, a raw score can be computed for each MSQ dimension. The raw score for each dimension is simply the algebraic sum of the final item value for all items in that dimension. The range of each raw dimension score is shown in Table 15-2.

3. Transformation of raw dimension scores to a 0 to 100 scale

   After the raw score for each MSQ dimension is computed, the each score is transformed to a 0 to 100 scale. The transformation formula for each dimension is provided in Table 15-2. The transformation process allows each dimension score to

reflect the percentage of the total possible score achieved (since 100 equal the highest score).

Table 15-1 Precoded and final item values for MSQ item responses

Response categories	Precoded items value	Final item value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Table 15-2 Raw score and transformation formula for each MSQ dimension

MSQ dimension	Item No.	Raw score range	Transformation formula
Role Function - Restrictive	1-7	7 to 42	((raw score − 7) × 100) / 35
Role Function - Preventive	8-11	4 to 24	((raw score − 4) × 100) / 20
Emotional Function	12-14	3 to 18	((raw score − 3) × 100) / 15

Handling of missing data:

In the event that responses on one or more items within a dimension are missing, a missing item value may be estimated using the average of the other items within the same dimension. If a respondent answered at least half of the items in a multi item scale (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated.

Appendix 3 Criteria for Identifying Laboratory Values of Potentially Clinically Significant

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	

Laboratory Tests	Criteria
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 4 Criteria for Identifying Vital Signs of Potentially Clinically Significant

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

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CT-14.8.5.1.2	Serious TEAEs by MedDRA SOC and PT in Japan (SS1)
CT-14.8.5.1.3	Serious TEAEs by MedDRA SOC and PT in Korea (SS1)
CT-14.8.5.2.1	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.5.2.2	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT in Japan (SS1)
CT-14.8.5.2.3	Potentially Drug-related Serious TEAEs by MedDRA SOC and PT in Korea (SS1)
CT-14.8.6.1.1	TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.6.1.2	TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT in Japan (SS1)
CT-14.8.6.1.3	TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT in Korea (SS1)

CT-14.8.6.2.1	Potentially Drug-related TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.6.2.2	Potentially Drug-related TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT in Japan (SS1)
CT-14.8.6.2.3	Potentially Drug-related TEAEs leading to discontinuation of the IMP by MedDRA SOC and PT in Korea (SS1)
CT-14.8.7.1.1	TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.7.1.2	TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT in Japan (SS1)
CT-14.8.7.1.3	TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT in Korea (SS1)
CT-14.8.7.2.1	Potentially Drug-related TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.7.2.2	Potentially Drug-related TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT in Japan (SS1)
CT-14.8.7.2.3	Potentially Drug-related TEAEs reported in at least 2% of subjects at Any Group by MedDRA SOC and PT in Korea (SS1)
CT-14.8.7.3.1	TEAEs by MedDRA SOC and PT in Age <65 years (SS1)
CT-14.8.7.3.2	TEAEs by MedDRA SOC and PT in Age >=65 years (SS1)
CT-14.8.7.3.3	TEAEs by MedDRA SOC and PT in Male (SS1)
CT-14.8.7.3.4	TEAEs by MedDRA SOC and PT in Female (SS1)
CT-14.8.7.3.5	TEAEs by MedDRA SOC and PT in using preventive migraine medication at baseline (SS1)
CT-14.8.7.3.6	TEAEs by MedDRA SOC and PT in not using preventive migraine medication at baseline (SS1)
CT-14.8.8.1	Injection Site Reaction TEAEs by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.8.2	Ophthalmic TEAEs of at least moderate severity by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.8.3	Drug-related Hepatic TEAEs by MedDRA SOC and PT, All Countries (SS1)

CT-14.8.8.4	Anaphylaxis and severe hypersensitivity reaction TEAEs by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.8.5	Cardiovascular-related TEAEs by MedDRA SOC and PT, All Countries (SS1)
CT-14.8.8.6	Non-Serious TEAEs Greater Than or Equal to 5% in Any Group by MedDRA SOC and PT, All Countries (SS1)
CT-14.9.1	Listing of Serious Adverse Events (SS1)
CT-14.9.2	Listing of Adverse Events leading to discontinuation of the IMP (SS1)
CT-14.9.3	Listing of Deaths (SS1)
CT-14.9.4	Listing of Injection Site Reaction Adverse Events (SS1)
CT-14.9.5	Listing of Ophthalmic Adverse Events of at least moderate severity (SS1)
CT-14.9.6	Listing of Drug-related Hepatic Adverse Events (SS1)
CT-14.9.7	Listing of Anaphylaxis and severe hypersensitivity reaction Adverse Events (SS1)
CT-14.9.8	Listing of Cardiovascular-related Adverse Events (SS1)
CT-14.10.1.1	Descriptive Statistics for Laboratory Values (Serum Chemistry) (SS1)
CT-14.10.1.2	Descriptive Statistics for Laboratory Values (Hematology) (SS1)
CT-14.10.1.3	Descriptive Statistics for Laboratory Values (Coagulation) (SS1)
CT-14.10.1.4	Descriptive Statistics for Laboratory Values (Urinalysis) (SS1)
CT-14.10.2.1	Incidences of PCS Abnormalities in Laboratory Tests (Serum Chemistry) (SS1)
CT-14.10.2.2	Incidences of PCS Abnormalities in Laboratory Tests (Hematology and Coagulation) (SS1)
CT-14.10.2.3	Incidences of PCS Abnormalities in Laboratory Tests (Urinalysis) (SS1)
CT-14.10.3.1	Listing of PCS Abnormalities in Serum Chemistry Laboratory Tests (SS1)
CT-14.10.3.2	Listing of PCS Abnormalities in Hematology and Coagulation Laboratory Tests (SS1)
CT-14.10.3.3	Listing of PCS Abnormalities in Urinalysis Laboratory Tests (SS1)
CT-14.10.4.1	Shift Table of Laboratory Values (Serum Chemistry) (SS1)

CT-14.10.4.2	Shift Table of Laboratory Values (Hematology) (SS1)
CT-14.10.4.3	Shift Table of Laboratory Values (Coagulation) (SS1)
CT-14.10.4.4.1	Shift Table of Laboratory Values (Urinalysis1) (SS1)
CT-14.10.4.4.2	Shift Table of Laboratory Values (Urinalysis2) (SS1)
CT-14.11.1	Descriptive Statistics for Vital Sign and Weight Values (SS1)
CT-14.11.2	Incidences of PCS Abnormalities in Vital Signs (SS1)
CT-14.11.3	Listing of PCS Abnormalities in Vital Signs Values (SS1)
CT-14.12.1	Descriptive Statistics for ECG Parameters (SS1)
CT-14.12.2	Shift Table of ECG Findings (Investigators ECG Interpretation) (SS1)
CT-14.12.3	Incidence of Categorical Changes in ECG Parameters (SS1)
CT-14.12.4	Listing of Categorical Changes in Electrocardiogram Evaluations (SS1)
CT-14.13.1	Injection Site Assessments - Injection-site Pain (SS1)
CT-14.13.2	Injection Site Assessments - Injection-site Erythema (SS1)
CT-14.13.3	Injection Site Assessments - Injection-site Induration (SS1)
CT-14.13.4	Injection Site Assessments - Injection-site Ecchymosis (SS1)
CT-14.13.5.1	Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) Assessment Outcome Responses (SS1)
CT-14.13.5.2	Subjects with Positive Responses for Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) Assessment (SS1)
CF-1	LS Mean Change from Baseline in Monthly Number of Migraine Days Using MMRM (FAS)
CF-2	LS Mean Change from Baseline in Monthly Number of Days with Use of Any Acute Headache Medication Using MMRM (FAS)
CF-3	LS Mean Change from Baseline in Monthly Number of Migraine Days in Subjects Not Receiving Concomitant Preventive Migraine Medication Using MMRM (FAS)
CF-4	LS Mean Change from Baseline in Monthly Number of Headache Days of at Least Moderate Severity Using MMRM (FAS)

PKT-X.1.4.1	Individual and Summary of Plasma Trough Concentration

Appendix 6 List of Subject Data Listings

PDATA-1.1	Subject Disposition (RS2)
PDATA-1.2	Analysis Population Flag (RS2)
PDEV-1	Major Protocol Deviations (RS2)
DEMOG-1.1	Demographics (RS2)
DEMOG-1.2	Initial Migraine Diagnosis Date (RS2)
DEMOG-1.3	Childbearing Potential (Females Only) (RS2)
PDATA-1.3	Medical History (RS2)
PDATA-1.4	Complications (RS2)
PDATA-1.5.1	Prior and Concomitant Medications and Therapy (RS2)
PDATA-1.5.2	Past Preventive Migraine Medications (RS2)
SMED-1.1	Study Drug Administration (RS2)
SMED-1.2	Extent of Exposure (RS2)
PDATA-1.6	Vital Signs Values (RS2)
PDATA-1.7.1	Electrocardiogram Measurement (RS2)
PDATA-1.7.2	Electrocardiogram Interpretation (RS2)
PDATA-1.7.3	Electrocardiogram Findings (RS2)
PDATA-1.7.4	Electrocardiogram Technical (RS2)
PDATA-1.8	Physical Examination Findings (RS2)
PDATA-1.9	Electronic Columbia-Suicide Severity Rating Scale (EC-SSRS) Assessment (RS2)
PDATA-1.10	Injection Site Assessment (RS2)
PDATA-1.11	Screen Failures (Screen Failure)

PDATA-1.12	Subjects Who Did Not Meet Inclusion Criteria or Meet Exclusion Criteria (Screen Failure)
PDATA-1.13	Pharmacokinetic Blood Draw Date and Times (RS2)
PDATA-1.14	Anti-drug Antibodies Blood Draw Date and Times (RS2)
PDATA-1.15	Biomarker Sampling Date and Times (RS2)
PDATA-1.16	Subjects Who Did Not Meet Inclusion Criteria or Meet Exclusion Criteria (RS2)
PDATA-1.17	Information on Subjects Lost to Follow-up (RS2)
EFF-1.1.1	Electronic Headache Diary Questionnaire - Questions List
EFF-1.1.2	Electronic Headache Diary Questionnaire - Results (RS2)
EFF-1.1.3	Electronic Headache Diary Questionnaire - Derived (RS2)
EFF-1.2.1	Migraine Disability Assessment (MIDAS) - Questions List
EFF-1.2.2	Migraine Disability Assessment (MIDAS) - Results (RS2)
EFF-1.3.1	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Questions List
EFF-1.3.2	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Results (RS2)
EFF-1.4.1	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Questions List
EFF-1.4.2	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Results (RS2)
EFF-1.5.1	Patient Health Questionnaire-9 (PHQ-9) - Questions List
EFF-1.5.2	Patient Health Questionnaire-9 (PHQ-9) - Results (RS2)
EFF-1.6.1	Work Productivity and Activity Impairment (WPAI) Questionnaire - Questions List
EFF-1.6.2	Work Productivity and Activity Impairment (WPAI) Questionnaire - Results (RS2)
EFF-1.7	Patients Global Impression of Change (PGIC) Scale (RS2)
AE-1.1	Treatment-Emergent Adverse Events (RS2)
AE-1.2	Prior to Treatment Adverse Events (RS2)
LAB-1.1	Serum Chemistry Laboratory Tests Results (RS2)

LAB-1.2	Hematology Laboratory Tests Results (RS2)
LAB-1.3	Coagulation Laboratory Tests Results (RS2)
LAB-1.4	Urinalysis Laboratory Tests Results (RS2)
LAB-1.5	Pregnancy Test Results (Females Only) (RS2)
PDATA-2.1	Subject Disposition (RS1)
PDATA-2.2	Analysis Population Flag (RS1)
PDEV-2	Major Protocol Deviations (RS1)
DEMOG-2.1	Demographics (RS1)
DEMOG-2.2	Initial Migraine Diagnosis Date (RS1)
DEMOG-2.3	Childbearing Potential (Females Only) (RS1)
PDATA-2.3	Medical History (RS1)
PDATA-2.4	Complications (RS1)
PDATA-2.5.1	Prior and Concomitant Medications and Therapy (RS1)
PDATA-2.5.2	Past Preventive Migraine Medications (RS1)
SMED-2.1	Study Drug Administration (RS1)
SMED-2.2	Extent of Exposure (RS1)
PDATA-2.6	Vital Signs Values (RS1)
PDATA-2.7.1	Electrocardiogram Measurement (RS1)
PDATA-2.7.2	Electrocardiogram Interpretation (RS1)
PDATA-2.7.3	Electrocardiogram Findings (RS1)
PDATA-2.7.4	Electrocardiogram Technical (RS1)
PDATA-2.8	Physical Examination Findings (RS1)
PDATA-2.9	Electronic Columbia-Suicide Severity Rating Scale (EC-SSRS) Assessment (RS1)
PDATA-2.10	Injection Site Assessment (RS1)

PDATA-2.13	Pharmacokinetic Blood Draw Date and Times (RS1)
PDATA-2.14	Anti-drug Antibodies Blood Draw Date and Times (RS1)
PDATA-2.15	Biomarker Sampling Date and Times (RS1)
PDATA-2.16	Subjects Who Did Not Meet Inclusion Criteria or Meet Exclusion Criteria (RS1)
PDATA-2.17	Post Treatment follow-up (RS1)
EFF-2.1.1	Electronic Headache Diary Questionnaire - Questions List
EFF-2.1.2	Electronic Headache Diary Questionnaire - Results (RS1)
EFF-2.1.3	Electronic Headache Diary Questionnaire - Derived (RS1)
EFF-2.2.1	Migraine Disability Assessment (MIDAS) - Questions List
EFF-2.2.2	Migraine Disability Assessment (MIDAS) - Results (RS1)
EFF-2.3.1	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Questions List
EFF-2.3.2	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Results (RS1)
EFF-2.4.1	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Questions List
EFF-2.4.2	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Results (RS1)
EFF-2.5.1	Patient Health Questionnaire-9 (PHQ-9) - Questions List
EFF-2.5.2	Patient Health Questionnaire-9 (PHQ-9) - Results (RS1)
EFF-2.6.1	Work Productivity and Activity Impairment (WPAI) Questionnaire - Questions List
EFF-2.6.2	Work Productivity and Activity Impairment (WPAI) Questionnaire - Results (RS1)
EFF-2.7	Patients Global Impression of Change (PGIC) Scale (RS1)
AE-2.1	Treatment-Emergent Adverse Events (RS1)
AE-2.2	Prior to Treatment Adverse Events (RS1)
LAB-2.1	Serum Chemistry Laboratory Tests Results (RS1)
LAB-2.2	Hematology Laboratory Tests Results (RS1)
LAB-2.3	Coagulation Laboratory Tests Results (RS1)

LAB-2.4 Urinalysis Laboratory Tests Results (RS1)