STATISTICAL ANALYSIS PLAN

A Multicenter, Randomized, Open-label Trial Evaluating the Long-term Safety and Tolerability of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
TEV-48125

Protocol No. 406-102-00003

A Multicenter, Randomized, Open-label Trial Evaluating the Long-term Safety and Tolerability of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Migraine

Statistical Analysis Plan

Version: 1.0
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List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
CM	Chronic migraine
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
HIT-6	6-Item Headache Impact Test
IGS	Immunogenicity Analysis set
IMP	Investigational medicinal product
IRT	Interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment
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 406-102-00003. 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 long-term safety and tolerability of subcutaneous (SC) administration of TEV-48125 (at 225 mg once monthly [except for a loading dose of 675 mg in chronic migraine (CM) patients] or at 675 mg every 3 months) as preventive treatment for CM or episodic migraine (EM) patients.

3 Trial Design

3.1 Type/Design of Trial

This is a multicenter, randomized, open-label trial in patients with CM or EM. The schematic of the trial design is shown in Figure 3.1-1.

The trial consists of a 4-week screening period, a 52-week treatment period, and a follow-up period of 225 days after the final dose of investigational medicinal product (IMP). In the trial, treatment period is defined as up to 4 weeks after the final dose of IMP. The trial has a follow-up period after the end of treatment to allow antidrug antibody (ADA) assessment to be performed.

After obtaining written informed consent from patients, the investigator will screen them for eligibility (Visit [V] 1/Screening). Subjects who meet all the inclusion criteria and do not fall under any of the exclusion criteria will be randomized at V2/Baseline in a 1:1 ratio to receive one of the 2 treatments shown below for CM or EM. In any treatment group, the IMP will be administered according to each dosing method specified below from V2/Baseline to V14/Month 12 and the final assessment will be performed at V15/End of treatment as an end of treatment visit. Subjects will return to the trial site for ADA assessment 225 days (the approximate equivalent of 5 half-lives of TEV-48125) after the final dose of IMP (V16/Follow-up). Subjects who withdraw from the trial will undergo evaluation at withdrawal and return to the trial site for ADA assessment 225 days after the final dose of IMP (V16/Follow-up).

The treatment groups in this trial are as follows:

[CM]

- TEV-48125 225 mg/1 month group[1]
- TEV-48125 675 mg/3 months group

[EM]

- TEV-48125 225 mg/1 month group
- TEV-48125 675 mg/3 months group

Those who complete or discontinue either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) will also be enrolled in this trial for the purpose of evaluating ADAs (subjects enrolled for ADA assessment only).

The investigator will obtain written informed consent to ADA assessment from these subjects and instruct them to return for ADA assessment 225 days after the final dose of IMP has been administered in either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) (V16/Follow-up). In this trial, the IMP will not be administered to subjects enrolled for ADA assessment only.

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 V16/Follow-up for the final assessment/observation. For subjects who become 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.

If a new drug application is filed based on the results of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) before the end of this trial, an interim analysis of this trial will be performed.

[1] including the loading dose of 675 mg

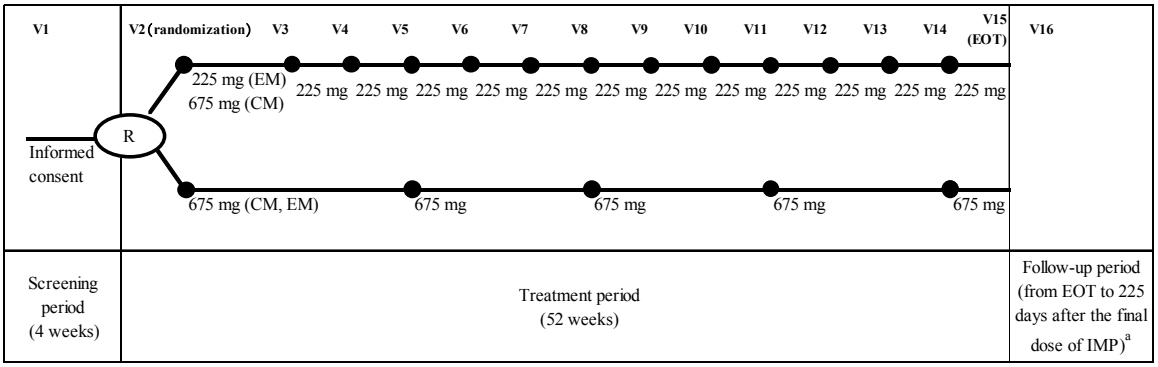

Figure 3.1-1 Trial Design Schematic

EOT = End of treatment; R = randomization.

[a]The follow-up period is defined as the period from EOT to 225 days after the final dose of IMP.

3.2 Trial Treatments

The IMP will be subcutaneously administered by clinical trial personnel responsible for administration of injections. The IMP will be administered once every 4 weeks (acceptable window: ± 5 days) for a total of 13 doses (at 225 mg once monthly [except for a loading dose of 675 mg in subjects with CM]) or every 12 weeks (acceptable window: ± 5 days) for a total of 5 doses (at 675 mg once every 3 months). For this trial, 1 month refers to 4 weeks. 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.

[CM]

- TEV-48125 225 mg/1 month group
  Subjects will receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL) at V2/Baseline and 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL) at each scheduled visit from V3/Month 1 through V14/Month 12.
- TEV-48125 675 mg/3 months group
  Subjects will receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL) at each scheduled visit of V2/Baseline, V5/Month 3, V8/Month 6, V11/Month 9, and V14/Month 12.

[EM]

- TEV-48125 225 mg/1 month group
  Subjects will receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL) at each scheduled visit from V2/Baseline through V14/Month 12.
- TEV-48125 675 mg/3 months group
  Subjects will receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL) at each

scheduled visit of V2/Baseline, V5/Month 3, V8/Month 6, V11/Month 9, and V14/Month 12.

At the time of each visit, the Interactive Response Technology (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 date and time of SC injections and their location will be recorded for each dosing visit.

The IMP will not be administered to subjects enrolled for ADA assessment only.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of 40 males or females with CM or EM aged 18 to 70 years, inclusive, will be enrolled in the trial. Of them, approximately 30 are expected to complete the trial. The enrollment procedure will be continued until the number of enrolled subjects reaches 40.

Up to 966 subjects who have completed or discontinued either of the phase 2b/3 trials in patients with CM or EM (Trials 406-102-00001 and 406-102-00002) will be enrolled in this trial solely for the purpose of ADA assessment (the IMP will not be administered to these subjects in this trial). Of these, approximately 644 subjects who have received TEV-48125 in either of the phase 2b/3 trials will undergo ADA assessment.

4 Sample Size

Sample size was not calculated by any statistical method.

In order to fully evaluate the long-term safety of TEV-48125 in Japanese patients, it is necessary to collect data from 100 Japanese patients who have completed a 1-year treatment with the drug at the same doses and regimens as those in the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) conducted in parallel with this trial (see Section 2.1 in the protocol). Assuming a 30% discontinuation rate in Japanese subjects in a multinational phase 3 long-term trial (Trial TV48125-CNS-30051), approximately 80 patients receiving TEV-48125 are expected to complete the multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050). To make up the difference (20 patients), assuming the same discontinuation rate of 30% in this trial (Trial 406-102-00003), it is estimated that 30 patients are needed. Considering the possibility that the discontinuation rate may exceed 30% in either the multinational phase 3 long-term trial or this trial, in order to ensure compliance with the criteria contained in the ICH E1 Guideline that 100 subjects complete a year of administration, it is considered necessary to enroll 40 new patients in this trial.

For the purpose of ADA assessment, up to 966 subjects who have completed or discontinued either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) in patients with CM or EM will be enrolled in this trial. Of these subjects, only those who have received TEV-48125 in either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) will be evaluated for ADAs in this trial. Therefore, ADA assessment will be performed in approximately 644 subjects (approximately 360 subjects and 284 subjects who have received TEV-48125 in Trial 406-102-00001 and Trial 406-102-00002, respectively).

5 Statistical Analysis Datasets

5.1 Analysis Sets

- Enrolled set (ES):
  Subjects from whom informed consent has been obtained
- Randomized set (RS):
  Randomized newly enrolled subjects in the ES
- Safety set (SS):
  Newly enrolled subjects in the RS who receive the IMP at least once
- Full Analysis set (FAS):
  Newly enrolled subjects in the SS who have at least 10 days of baseline and post baseline efficacy assessment data in the electronic headache diary
- Pharmacokinetic Analysis Set 1 (PKS 1):

Of the subjects who were enrolled in the phase 2b/3 trial in EM patients (Trial 406-102-00002) prior to the suspension of that trial and have rolled over to the present trial, those who received at least one dose of TEV-48125 in Trial 406-102-00002 and in whom date and time of blood sampling for plasma drug concentration is recorded for at least one postdose time point in the present trial will be included.

- Pharmacokinetic Analysis Set 2 (PKS 2):

  Of the subjects who are newly enrolled in the present trial, those who were enrolled in the phase 2b/3 trial in CM patients (Trial 406-102-00001) and have rolled over to the present trial, or those who were enrolled in the phase 2b/3 trial in EM patients (Trial 406-102-00002) after the resumption of that trial and have rolled over to the present trial, those who received at least one dose of TEV-48125 in either the present trial, Trial 406-102-00001, or Trial 406-102-00002 and in whom date and time of blood sampling for plasma drug concentration is recorded for at least one postdose time point in the present trial will be included.

- Immunogenicity Analysis Set 1 (IGS 1):

  Of the subjects who were enrolled in the phase 2b/3 trial in EM patients (Trial 406-102-00002) prior to the suspension of that trial and have rolled over to the present trial, those who received at least one dose of TEV-48125 in Trial 406-102-00002 and in whom date and time of blood sampling for serum ADA assessment is recorded for at least one postdose time point in the present trial will be included.

- Immunogenicity Analysis Set 2 (IGS 2):
  Of the subjects who were newly enrolled in the present trial, those who were enrolled in the phase 2b/3 trial in CM patients (Trial 406-102-00001) and have rolled over to the present trial, or those who were enrolled in the phase 2b/3 trial in EM patients (Trial 406-102-00002) after the resumption of that trial and have rolled over to the present trial, those who received at least one dose of TEV-48125 in either the present trial, Trial 406-102-00001, or Trial 406-102-00002 and in whom date and time of blood sampling for serum ADA assessment is recorded for at least one postdose time point in the present trial will be included.

- Enrolled Set for ADA Assessment Only:
  Subjects from whom informed consent was obtained after V5/End of treatment or withdrawal in either of the phase 2b/3 trials (Trials 406-102-00001 or 406-102-00002)

5.2 Handling of Missing Data

In the safety analysis, the objective of this trial, and in pharmacokinetic analysis, no imputation will be performed for missing data.

6 Primary and Secondary Outcome Variables:

There are no primary and secondary outcome variables.

7 Disposition and Demographic Analysis

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

7.1 Subject Disposition

For the Enrolled Set for ADA Assessment Only, the number of subjects from whom informed consent was obtained and who completed the follow-up visit will be provided for the overall population and by treatment group (TEV-48125 675[225]/225/225 mg group, TEV-48125 675 mg/placebo/placebo group, or placebo group) for each of the previous trials (Trial 406-102-00001 and Trial 406-102-00002) and for the 2 trials combined.

For the ES, the number of subjects from whom informed consent has been obtained and the number of screen failure subjects and of randomized subjects will be provided. For the RS, 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, and who complete the follow-up visit will be summarized for the overall population and by treatment group. The primary reason for discontinuation will also be summarized for the overall population and by treatment group.

The number and percentage of subjects who are included in the SS and FAS, and who are excluded from the SS and FAS will be summarized for the overall population and by treatment group. The number of subjects who are included in the PKS 1, IGS 1, PKS 2, and IGS 2 will be summarized for the overall population and by treatment group (pervious and present studies).

The treatment groups in this study will be comprised of a 225 mg monthly group (TEV-48125 225 mg/1 month group for CM and EM patients) and a 675 mg quarterly group (TEV-48125 675 mg/3 months group for CM and EM patients).

7.2 Demographic and Baseline Characteristics

Data will be summarized for the overall population and by treatment group for the RS, PKS 1, and PKS 2. For the PKS 2, data will also be summarized by treatment group and migraine subtype. Data will be summarized for the overall population for the IGS 1 and IGS 2.

The following demographic and baseline characteristics will be summarized. 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), sex (male, female)
- 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. 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 treatment group for the RS.

The following baseline disease evaluation will be summarized. Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using 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
- 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 Headache-Related Data 9.1.1) 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 8.1.

7.5 Prior and Concomitant Medications

Data will be summarized for the overall population and by treatment group for the RS.

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 up to V15/EOT or withdrawal.

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 for the overall population and by treatment group for the RS.

8 Safety Analysis

The SS will be used for all safety analyses. Summaries will be presented for overall population and by treatment group unless specified otherwise. Descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

8.1 Extent of Exposure

Duration of treatment (days treated) is the number of days on treatment based on the first dose of IMP day and 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, ≥3 doses, etc, will be summarized by treatment group. Duration of treatment (days) will be summarized using descriptive statistics and frequency distribution for the cumulative categories (>0 months, ≥3 months, ≥6 months, ≥9 months, and ≥13 months). One month will be defined as 28 days. The total exposure of IMP allocated at each visit (from V2/Baseline to V14/Month 12) will also be summarized by treatment group.

8.2 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 5% of subjects in overall population

The above summaries will also be prepared for TEAEs potentially drug related. In addition, TEAEs will be summarized by age (<65, ≥65), sex (male, female) 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

8.3 Clinical Laboratory Data

Descriptive statistics will be calculated for clinical laboratory data and changes from baseline at each time point (V4/Month 2, V6/Month 4, V8/Month 6, V10/Month 8, V12/Month 10, V14/Month 12, V15/EOT, 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.

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.

8.4 Vital Sign and Weight Data

Descriptive statistics will be calculated for vital sign and weight measurements and changes from baseline at each time point (For vital sign: from V3/Month 1 to V15/EOT and final evaluation; For weight: V3/Month 1, V4/Month 2, V5/Month 3, V7/Month 5, V8/Month 6, V13/Month 11, V14/Month 12, V15/EOT, final evaluation in the treatment period, and V/16/Follow-up).

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 2.

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 other than V/16/Follow-up). Summaries of PCS values will include all post-baseline data.

8.5 Physical Examination Data

A list will be prepared for subjects with physical examination.

8.6 Electrocardiogram Data

Descriptive statistics will be calculated for electrocardiogram (ECG) measurements and changes from baseline at each time point (V15/EOT 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.

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.

Baseline will be the last value prior to the first dose of IMP. V15/EOT visit will be the Nominal visits. Final evaluation will be the last observed all post-baseline data (including scheduled, unscheduled and withdrawal visits). Worst value will also be derived using all post-baseline data.

8.7 Injection Site Reactions

For severities of the injection site reactions (erythema, induration, ecchymosis, and pain), frequency distributions will be obtained by IMP administration visit (for 225 mg monthly group: from V2/Baseline to V14/Month 12; for 675 mg quarterly group: V2/Baseline, V5/Month 3, V8/Month 6, V11/Month 9, and V14/Month 12) and time point (immediately postdose and 1 hour postdose). Overall population will be calculated only for V2/Baseline, V5/Month 3, V8/Month 6, V11/Month 9, and V14/Month 12.

8.8 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.

9 Efficacy Analysis

The FAS will be used for all efficacy analyses. Summaries will be presented for overall population and by treatment group unless specified otherwise. Descriptive statistics will include number of subjects, mean, SD, median, minimum, and maximum.

9.1 Headache-Related Data

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

1) Number of migraine days
2) Number of headache days of at least moderate severity
3) Number of headache days of any severity
4) Number of days with use of any acute headache medications
5) Number of subjects discontinuing concomitant preventive migraine medications during the treatment period
6) Number of days with nausea or vomiting
7) Number of days with photophobia and phonophobia

The endpoints 1) and 2) during the 4-week period after Visits 2, 3, 4, 7, and 13 (ie, for Months 1, 2, 3, 6, and 12) will be summarized by visit/month. Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented. The means ± SDs of monthly change from baseline values will be plotted by month. In addition, proportion of subjects reaching at least 50%, 75%, and total (100%) reduction in the number of migraine days (and headache days of at least moderate severity) during the 4-week period after Visits 2, 3, 4, 7, and 13 (ie, for Months 1, 2, 3, 6, and 12) will be presented by visit/month. The 95% confidence interval of the responder rate will be calculated using Clopper-Pearson method. Furthermore, proportion of subjects reaching at least 50%, 75%, and total (100%) reduction in the number of migraine days (and headache days of at least moderate severity) during the 4-week period after Visit 4 (ie, Month 3) and for whom this level of effect is sustained during the 4 week periods after Visits 7 and 13 (ie, for Months 6 and 12), and the 95%

confidence intervals will be presented by visit/month. Missing data of evaluation will not be imputed.

The endpoints 3), 4), 6), and 7) during the 4-week period after Visits 2, 3, 4, 7, and 13 (ie, for Months 1, 2, 3, 6, and 12) will be summarized by visit/month. Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

For the endpoint 5), the proportion of subjects discontinuing concomitant preventive migraine medications during the treatment period for those who used concomitant preventive migraine medications and the 95% confidences interval will be summarized.

9.1.1 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 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 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, 3, 4, 7, and 13 (ie, for Months 1, 2, 3, 6, and 12) will be derived and normalized to 28 days (see the following formula), respectively. If a subject is randomized to the 675 mg quarterly group, visit day will be used as dose day (except for Visit 2). 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.

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

9.2 Other Than Headache-Related Data

The efficacy endpoints other than headache-related data will be collected using Electronic Patient-Reported Outcomes (ePRO).

9.2.1 Six-Item Headache Impact Test

The 6-Item Headache Impact Test (HIT-6) total score for CM subjects will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

Frequency distributions will be provided by grade in each time points for each item of HIT-6.

The HIT-6 total score is obtained from summation of the 6 question points. Each question is answered on the scale ranging with the following response options: 6 points (never), 8 points (rarely), 10 points (sometimes), 11 points (very often), and 13 points (always). If one or more items are missing, then the total score will be treated as missing data.

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.

9.2.2 Migraine Disability Assessment

The Migraine Disability Assessment (MIDAS) total score for EM subjects will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

Frequency distributions will be provided by MIDAS grade in each time points.

The MIDAS total score and MIDAS grade will be derived based on Attachment 3 in the protocol.

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.

9.2.3 Migraine-Specific Quality of Life Questionnaire

The transformed scores for the 3 domains (ie, Role Function-Restrictive, Role Function-Preventive, and Emotional Function) of Migraine-Specific Quality of Life (MSQOL) will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

The scoring instructions 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.

9.2.4 EuroQol-5 Dimension, 5 Response Level Version Questionnaire

Frequency distributions will be provided by scale (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems) and by time points (baseline, V8/Month 6, V14/Month 12, and final evaluation) for each domain (mobility, self-care, usual activities, pain/discomfort, and mood) of the EuroQol-5 Dimension, 5 Response Level Version (EQ-5D-5L) questionnaire. The VAS score will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

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.

9.2.5 Patient Global Impression of Change

The number and percentage of Patient Global Impression of Change Scale (PGIC) responders (subjects with PGIC scores of 5 to 7) and the 95% confidence interval will be provided for each time point (V3/Month 1, V5/Month 3, V8/Month 6, V11/Month 9, V14/Month 12, and final evaluation). Frequency distributions will also be provided by original response (scores: 1 to 7) at each time point.

Each visit will be the Nominal visits. Final evaluation will be the last observed all post-baseline data.

9.2.6 Two-Item Patient Health Questionnaire and Nine-Item Patient Health Questionnaire

The total score as measured by the 9-Item Patient Health Questionnaire (PHQ-9) will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

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.

9.2.7 Work Productivity and Activity Impairment Questionnaire

The following each score (in percentages) will be summarized by time point (baseline, V8/Month 6, V14/Month 12, and final evaluation). Descriptive statistics of values and changes from baseline and 95% confidence intervals of the mean changes from baseline will be presented.

The scores (in percentages) will be derived based on the Work Productivity and Activity Impairment (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: $\frac{Q6}{10} \times 100$

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.

10 Pharmacokinetic Analyses

10.1 Endpoint

Plasma TEV-48125 concentration

10.2 Dataset for Analysis

Pharmacokinetic analysis sets (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.
- Only for the pharmacokinetic analysis, subjects enrolled for ADA assessment only (roll-over subjects from 406-102-00001 or 406-102-00002) will be re-assigned to "TEV-48125 225 mg/1 month group" or "TEV-48125 675 mg/3 months group" based on the randomized groups in 406-102-00001 or 406-102-00002 as below.

Table 10-1 Assignment of Subjects to Treatment Groups

Trial	Disease Subtype	Treatment Group in 406-102-00001 or 406-102-00002	Treatment Group in the present trial
406-102-00001	CM	TEV-48125 675/225/225 mg group	TEV-48125 225 mg/1 month group
		TEV-48125 675 mg/placebo/placebo group	TEV-48125 675 mg/3 months group
406-102-00002	EM	TEV-48125 225/225/225 mg group	TEV-48125 225 mg/1 month group
		TEV-48125 675 mg/placebo/placebo group	TEV-48125 675 mg/3 months group

10.4 Statistical Analysis Method

Concerning 10.1 Endpoint, separately for PKS 1 and PKS 2, descriptive statistics will be calculated at each blood sampling time point for the entire set (overall), by treatment group, and by disease subtype (CM or EM) and treatment group. Descriptive statistics to be calculated will 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

For the new drug application for TEV-48125, one interim analysis will be performed using interim data locked on 20 Dec 2019.

14 Changes in the Planned Analyses

・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.

2 Otsuka Pharmaceutical Co., Ltd. Manual standard practice for noncompartmental pharmacokinetic analysis. Version 1.0, issued 24 Dec 2015.

Appendix 1 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	
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 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	Increase of ≥ 15 mmHg

	≤ 50 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 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 for CM subjects	A2 = Yes
	2 for EM 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

Appendix 4 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.

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EFF-3.2	Migraine Disability Assessment (MIDAS) - Results (Indication: Episodic Migraine (EM)) (RS)

EFF-4.1	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Questions List
EFF-4.2	Migraine-Specific Quality of Life (MSQOL) Questionnaire - Results (RS)
EFF-5.1	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Questions List
EFF-5.2	EuroQoL-5 Dimension (EQ-5D-5L) Questionnaire - Results (RS)
EFF-6.1	Subject Health Questionnaire-9 (PHQ-9) - Questions List
EFF-6.2	Subject Health Questionnaire-9 (PHQ-9) - Results (RS)
EFF-7.1	Work Productivity and Activity Impairment (WPAI) Questionnaire - Questions List
EFF-7.2	Work Productivity and Activity Impairment (WPAI) Questionnaire - Results (RS)
EFF-8	Patients Global Impression of Change (PGIC) (RS)
AE-1	Treatment-Emergent Adverse Events (RS)
AE-2	Prior to Treatment Adverse Events (RS)
AE-3	Adverse Events (Enrolled Set for ADA Assessment Only)
AE-4	Subjects with Serious Adverse Events (Enrolled Set for ADA Assessment Only)
AE-5	Subjects with Deaths (Enrolled Set for ADA Assessment Only)
AE-6	Subjects with Ophthalmic Adverse Events of at Least Moderate Severity (Enrolled Set for ADA Assessment Only)
AE-7	Subjects with Drug-related Hepatic Adverse Events (Enrolled Set for ADA Assessment Only)
AE-8	Subjects with Anaphylaxis and Severe Hypersensitivity Reaction Adverse Events (Enrolled Set for ADA Assessment Only)
AE-9	Subjects with Cardiovascular-related Adverse Events (Enrolled Set for ADA Assessment Only)
LAB-1	Serum Chemistry Laboratory Tests Results (RS)
LAB-2	Hematology Laboratory Tests Results (RS)
LAB-3	Coagulation Laboratory Tests Results (RS)
LAB-4	Urinalysis Laboratory Tests Results (RS)
LAB-5	Pregnancy Test Results (Females Only) (RS)