CLINICAL STUDY PROTOCOL

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

CLINICAL PROTOCOL

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

Protocol No.: 406-102-00003

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	PAREXEL International Global Medical Services, Pharmacovigilance E-mail address: IRE_406-102-00003@otsuka.jp
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Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: TEV-48125	Protocol No.: 406-102-00003
Protocol Title:	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
Clinical Phase/ Trial Type:	Phase 3 long-term safety trial
Treatment Indication:	Preventive treatment of chronic migraine (CM) and episodic migraine (EM)
Objectives:	To evaluate the long-term safety and tolerability of subcutaneous administration of TEV-48125 (at 225 mg once monthly [except for a loading dose of 675 mg for CM patients] or at 675 mg every 3 months) for the preventive treatment of CM and EM patients
Trial Design:	A multicenter, randomized, open-label trial
Subject Population:	(1) 40 males or females with CM or EM, aged 18 to 70 years, inclusive. (2) 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, respectively) (These subjects will be enrolled solely for the purpose of antidrug antibody (ADA) assessment in this trial and no IMPs will be administered to these subjects in this trial; hereinafter referred to as subjects enrolled for ADA assessment only). To these subjects enrolled for ADA assessment only, none of the following information in this synopsis, excluding that under the headings "Trial sites" and "Overall trial period," will apply [information presented under these headings is categorized as (1) or (2) according to its applicability to the subject population (1) or (2) as defined above].
Inclusion/Exclusion Criteria:	Main inclusion criteria are as follows: • Patient has a history of migraine (according to The International Classification of Headache Disorders, third edition [beta version] [ICHD-3 beta] criteria [Classification Committee of the International Headache Society 2013]) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 beta diagnosis) for ≥ 12 months prior to giving informed consent • Patient fulfills all the following criteria for CM or EM in

	baseline information collected during the 28-day screening period: [EM] – Headache occurring on ≥ 4 and ≤ 14 days – Fulfilling any of the criteria for migraine listed below on ≥ 4 days [CM] – Headache occurring on ≥ 15 days – Fulfilling any of the criteria for migraine listed below on ≥ 8 days Criteria for migraine – ICHD-3 beta diagnostic criteria C and D for 1.1 Migraine without aura – ICHD-3 beta criteria B and C for 1.2 Migraine with aura – Probable migraine (a migraine subtype where only 1 migraine criterion is missing) – The patient used a triptan or ergot derivative to treat an established headache • Not using preventive migraine medications (prohibited or restricted medications, see Table 4.1.1-1 and Table 4.1.2-1) for migraine or other medical conditions (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medication (restricted medications, see Table 4.1.2-1) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent. • The patient demonstrates compliance with the electronic headache diary during the screening period by entry of headache data on a minimum of 24 of 28 days (≥ 85% diary compliance) and the entered data is judged appropriate by the investigator. Main exclusion criteria are as follows: • Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease, considered clinically significant in the judgment of the investigator
Trial Sites:	(1) Approximately 10 sites in Japan (planned) (2) Approximately 60 sites (approximately 52 sites in Japan and approximately 8 sites in South Korea) (planned)
Investigational Medicinal Products, Dose, Dosage	The trial personnel responsible for administration of injections will administer TEV-48125 subcutaneously once

Regimen, Treatment Period, Formulation, Mode of Administration:	every 4 weeks for a total of 13 doses to subjects who are to be treated once monthly or once every 12 weeks for a total of 5 doses to subjects who are to be treated once every 3 months as instructed below. For this trial, 1 month refers to 4 weeks. [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 Visit (V) 2 /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.
Trial Assessments:	Efficacy: Electronic headache diary, 6-Item Headache Impact Test (HIT-6) (for CM subjects only), Migraine Disability Assessment (MIDAS) questionnaire (for EM subjects only), 2-Item Patient Health Questionnaire/9-Item Patient Health Questionnaire (PHQ-2/PHQ-9), Migraine-Specific Quality of Life (MSQOL) questionnaire, EuroQol-5 Dimension, 5 response level version (EQ-5D-5L) questionnaire, Patient Global Impression of Change (PGIC) scale, Work Productivity and Activity Impairment (WPAI) questionnaire Safety: Adverse events (AEs), clinical laboratory tests, physical examination, weight, vital signs, 12-lead electrocardiogram (ECG), electronic Columbia-Suicide Severity Rating Scale (eC-SSRS), injection site reaction assessments, urine human chorionic gonadotropin (HCG) test (women of childbearing potential [WOCBP] only), prior medication or therapy, and concomitant medication or therapy

	Pharmacokinetics: Blood sampling for measurement of plasma drug concentrations Screening/Other: Height, serum HCG test (WOCBP only), follicle-stimulating hormone (FSH) test (women at least 12 months postmenopausal only), and blood sampling for ADA assessment, blood sampling for pharmacogenomic assessment, and blood/urine collection for biomarker assessments
Criteria for Evaluation:	Safety endpoints: AEs, clinical laboratory tests, 12-lead ECGs, physical examination, vital signs, weight, injection site reaction (erythema, induration, ecchymosis, and pain) assessments (including severity), and eC-SSRS Efficacy endpoints: • Number of migraine days • Number of headache days of at least moderate severity • Number of headache days of any severity • Number of days with use of any acute headache medications • Number of subjects discontinuing concomitant preventive migraine medications during the treatment period • Number of days with nausea or vomiting • Number of days with photophobia or phonophobia • HIT-6 (for subjects with CM only) • MIDAS (for subjects with EM only) • MSQOL • EQ-5D-5L • PGIC • PHQ-2 and PHQ-9 • WPAI
Statistical Methods:	[Safety analysis] Safety endpoint data will be summarized overall and by treatment group in the safety analysis set. [Rationale for Target Sample Size] Sample size was not calculated by any statistical method. 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. 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 International Council for Harmonisation E1 Guideline that 100 subjects complete a year of administration, it is considered necessary to enroll 40 new patients in this trial.
Trial Duration:	Overall trial period [for both (1) and (2)]: Aug 2017 through Sep 2020 (planned) Planned trial participation period for individual subjects (1): approximately 589 days (Screening period of 4 weeks [28 days], treatment period of 52 weeks [364 days], and follow-up period of approximately 197 days) Planned trial participation period for individual subjects (2): approximately 197 days (follow-up period only)

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Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CBC	Complete blood count
CGRP	Calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Science
CM	Chronic migraine
C_{max}	Maximum (peak) plasma concentration of the drug
CRF	Case report form
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EDC	Electronic data capture
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid
EM	Episodic migraine
ePRO	Electronic patient-reported outcomes
EOT	End-of-treatment (visit)
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
ES	Enrolled set
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIT-6	6-Item Headache Impact Test
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3 beta	The International Classification of Headache Disorders, third edition (beta version)
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IgG	Immunoglobulin G
IGS	Immunogenicity analysis set
IMP	Investigational medicinal product
INR	International normalization ratio
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous
MIDAS	Migraine Disability Assessment
MSQOL	Migraine-Specific Quality of Life

Abbreviation	Definition
NOAEL	No-observed-adverse-effect level
PEF	Peak Expiratory Flow
PGIC	Patient Global Impression of Change
PHQ-2	2-Item Patient Health Questionnaire
PHQ-9	9-Item Patient Health Questionnaire
PKS	Pharmacokinetic analysis set
PQC	Product quality complaint
RNA	Ribonucleic acid
RS	Randomized set
SAE	Serious adverse event
SC	Subcutaneous
SS	Safety set
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) plasma concentration
ULN	Upper limit of normal
V	Visit
WPAI	Work Productivity and Activity Impairment
WOCBP	Women of childbearing potential
YLD	Year lived with disability

1 Introduction

1.1 Pathology and Treatment of Migraine

Migraine is a prevalent condition characterized by attacks of headache (moderate to severe pain intensity, unilateral location, and/or pulsating quality) and associated symptoms (such as nausea, photophobia, or phonophobia). Global Burden of Disease studies 2015 rank migraine as the seventh highest cause of years lived with disability (YLDs) and as the third highest cause of YLDs for ages 15 to 49 years, suggesting that the disease not only imposes a considerable disability burden on the daily and social lives of affected individuals but it also causes a serious social loss.[1]

Episodic migraine (EM) and chronic migraine (CM) are 2 common forms of migraine. Individuals with EM have headaches on less than 15 days per month,[2] while those with CM present with headaches on 15 or more days per month and have migraine on at least 8 days per month.[3] Approximately 3% of individuals with EM evolve, in any given year, to a significantly more disabling condition called CM.[4,5]

Although the pathophysiology of migraine has yet to be fully elucidated, it is believed that a certain stimulus works on the perivascular trigeminal axon, leading to the release of vasoactive neuropeptides, which act as neurotransmitters, including substance P and calcitonin gene-related peptide (CGRP), from nerve terminals and that this in turn triggers neurogenic inflammation around dura mater, contributing to the production of pain.[6,7,8] CGRP is thus involved in the pathophysiology of migraine.[6] Inhibition of CGRP has demonstrated efficacy in the treatment of EM and CM.[9,10]

Pharmacotherapeutic management of migraine consists of acute treatment and preventive treatment. The goals of acute treatment are to rapidly and certainly relieve attacks of migraine and restore the patient's ability to function. On the other hand, the goals of preventive treatment are: 1) to reduce the frequency, severity, and duration of headache; 2) to improve response to acute treatment; and 3) to improve life functions and reduce disabilities in daily life.[11] Currently available drug therapies for preventive treatment of migraine include antiepileptic drugs, beta-blockers, antidepressants, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers. Medications covered by Japanese health insurance for preventive treatment of migraine include lomerizine, valproic acid, propranolol, and dihydroergotamine, for which there are varying response rates in their ability to prevent migraine.

1.2 TEV-48125

TEV-48125 (also known as PF-04427429, RN307, or LBR-101) is a fully humanized immunoglobulin G (IgG) 2a/kappa monoclonal antibody derived from a murine precursor. TEV-48125 is a potent, selective CGRP binder and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. TEV-48125 is specific for CGRP and does not bind to the closely related family members amylin, calcitonin, or adrenomedullin peptides. Two mutations were introduced into the constant region of the TEV-48125 heavy chain to limit antibody effector functions. This loss of function prevents TEV-48125 from stimulating antibody-dependent cell-mediated cytotoxicity and triggering complement-mediated lysis; complement-mediated lysis can lead to unwanted consequences such as cell lysis, opsonization, and cytokine release and inflammation.[12,13] With a different mechanism of action from existing migraine prophylactics, TEV-48125 has acceptable tolerability, as confirmed from both nonclinical and clinical data, and a long plasma elimination half-life ($t_{1/2}$), thus representing a promising therapeutic candidate for the preventive treatment of migraine, which is expected to reduce dosing frequency compared to existing counterparts and provide an additional treatment option.

1.3 Nonclinical Data

In vivo pharmacology studies of TEV-48125 in animal models indicate that TEV-48125 prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare response in cynomolgus monkeys.

Safety pharmacology parameters of TEV-48125 were assessed in the toxicology studies in Sprague Dawley rats and cynomolgus monkeys and a separate cardiovascular safety pharmacology study in male cynomolgus monkeys. There were no treatment-related changes in electrocardiograms (ECGs) and heart rates in the 1- and 3-month toxicity studies, and a single intravenous (IV) dose of TEV-48125 at 100 mg/kg did not result in changes in cardiovascular parameters or body temperature in monkeys. Additionally, no target organ toxicity was identified. In these referenced studies, the no-observed-adverse-effect level (NOAEL) ranged from 100 to 300 mg/kg dosed either intravenously or subcutaneously. In a 3-month monkey study, perivascular inflammation of the ciliary artery was observed in a few animals at doses ≥ 100 mg/kg. The inflammation was suspected to be the result of immune complex formation/deposition from the monkeys' immunogenic response to the drug (TEV-48125). In the 6-month chronic toxicity study in monkeys following once-weekly subcutaneous (SC) dosing at dosage levels of up to 300 mg/kg/week, reaching high exposure throughout the study, no microscopic findings

were noted in any of the organs, including the ciliary vessels of the eyes, and the NOAEL of the chronic toxicity study was determined to be the highest dose tested, 300 mg/kg/week. Thus, it is believed that in view of the low frequency (ie, observed in very few animals) and minimal severity, the finding (perivascular inflammation) that was only recorded in the 3-month toxicity study, and had been resolved during the recovery period, is an incidental finding.

The pharmacokinetics of TEV-48125 in animals (rats and monkeys) is the same as that of a typical humanized IgG2 antibody, with low mean plasma clearance, low volume of distribution at steady state, and a long $t_{1/2}$. The maximum observed plasma concentration (C_{max}) and the area under the plasma concentration-time curve increased linearly across doses following single and repeated once-weekly dosing. No gender differences in exposure were observed in rats or monkeys.

Additionally, reproductive and developmental toxicity studies in rabbits and rats with TEV-48125 were conducted and completed. Preliminary data suggest that weekly dosing with TEV-48125 was well tolerated and did not induce any obvious maternal toxicity at any dose level. No apparent evidence of embryo-fetal toxicity was noted in any dose group.

Overall, no toxicological concerns were identified following up to 6 months of dosing to the experimental animals.

1.4 Clinical Data

To date, TEV-48125 has been studied in seven phase 1 trials in healthy adults and two phase 2b trials in migraine patients. In total, 532 subjects (166 healthy adults and 366 migraine patients) received at least 1 dose of TEV-48125 via IV or SC administration. Currently, 3 multinational phase 3 trials (Trials TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051) to further evaluate the efficacy, safety, and tolerability of dose regimens of TEV-48125 for the preventive treatment of CM or EM are ongoing.

1.4.1 Clinical Pharmacology Trials

A total of 166 subjects received at least 1 dose of TEV-48125 across 7 completed phase 1 trials at doses ranging from 0.2 through 2000 mg. Trials included 2 single-dose-escalation pharmacokinetic and pharmacodynamic trials in healthy adult men (Trials B0141001 and B0141002); a 2-cohort, placebo-controlled, crossover trial to examine the acute effects administration of TEV-48125 on capsaicin flare response in healthy adult men (Trial B0141006); a parallel-group, repeat-dose trial of TEV-48125 in healthy adult men and women (Trial B0141007); a single-dose trial evaluating the safety, tolerability,

and pharmacokinetics of doses up to 2000 mg administered to healthy adult women (Trial LBR-101-008); a single-dose trial comparing the safety, tolerability, absolute bioavailability, and pharmacokinetics of SC and IV TEV-48125 in healthy adult men and women (Trial LBR-101-011); and a trial evaluating the pharmacokinetics, safety, and tolerability of a single SC administration of TEV-48125 in healthy Japanese and Caucasian adult men and women (Trial TV48125-PK-10078).

Based on noncompartmental analysis, TEV-48125 exposure increases with dose in a more than dose-proportional manner from 225 to 900 mg following SC administration. The time to maximum (peak) plasma concentration (t_{max}) following SC administration at 225 to 900 mg ranged from 5 to 7 days with the dose having no observed impact on t_{max}. The mean $t_{1/2}$ following SC administration ranged from 32.23 to 36.15 days with no impact of the dose observed.

TEV-48125 was well tolerated with favorable safety profile. The treatment-emergent adverse events (TEAEs) reported in the phase 1 trials were predominantly mild or moderate in severity. Neither a specific "pattern of adverse events (AEs)" that was thought to be associated with a dose of TEV-48125 nor a maximally tolerated dose was identified. There were no deaths. One serious adverse event (SAE) reported as "thoracic aortic aneurysm aggravated" in an individual receiving a single IV 300-mg TEV-48125 dose resolved.

TEV-48125 was not associated with any clinically relevant patterns of change in vital signs (systolic and diastolic blood pressure, temperature, and heart rate) or cardiac conduction and repolarization (P-R interval, QT interval corrected for heart rate using Bazett's and Fridericia's formulas) measured by frequent 12-lead ECGs. No changes in liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and alkaline phosphatase [ALP]) or differences between TEV-48125 and placebo in hematological parameters, tests assessing renal function, electrolytes, or urinalysis has been observed in any of the phase 1 trials.

1.4.2 Clinical Safety and Efficacy Trials

The efficacy, safety, tolerability, and pharmacokinetics of TEV-48125 were evaluated in migraine patients in two phase 2b trials (Trial LBR-101-021 and Trial LBR-101-022). The first trial (Trial LBR-101-021) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial using TEV-48125 (2 dose levels) in 264 patients with CM. Following a 28-day run-in period, participants were randomized and treated SC once monthly for 3 months. One TEV-48125 group received a first dose of 675 mg followed by 225 mg on the subsequent 2 months. The other TEV-48125 group received

900 mg per month. The mean change in headache hours relative to baseline for each TEV-48125 dose group showed a statistically significant reduction in headache hours compared to the placebo group at 3 months (primary endpoint) and reductions also at 1 and 2 months. Both doses were also superior to placebo for the secondary endpoint (decrease in the number of days with moderate or severe headache at 3 months). At the doses tested, TEV-48125 was well tolerated, and no investigational medicinal product (IMP)-related SAEs were reported. Most TEAEs were mild or moderate. No safety signals were observed in the clinical laboratory tests, vital signs, physical examination, or ECGs.

The other phase 2b trial (Trial LBR-101-022) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial using TEV-48125 (2 dose levels) in 297 patients with EM. Following a 28-day run-in period, subjects were randomized and treated subcutaneously once monthly for 3 months. Two doses of TEV-48125 were tested, 225 mg given monthly for 3 months, and 675 mg given monthly for 3 months. The mean change in number of migraine days relative to baseline for each TEV-48125 dose group showed a statistically significant reduction in migraine days compared to the placebo group at 3 months (primary endpoint), and reductions also at 1, and 2 months. Differences in the secondary and exploratory endpoints compared to the placebo group were also seen throughout the trial. Both doses were well tolerated, and no IMP-related SAEs were reported. Most TEAEs were mild or moderate and the lowest dose had a numerically lower number of subjects with adverse events relative to placebo. No safety signals were observed in the clinical laboratory tests, vital signs, physical examination, or ECGs.

1.5 Known and Potential Risks and Benefits

Identified risks (adverse drug reactions) of TEV-48125 include injection site erythema, administration site pain, injection site pain, injection site pruritus, injection site dermatitis, infusion-related reaction, and drug hypersensitivity. Potential risks for TEV-48125 are perivascular inflammation; development of antidrug antibodies (ADAs); liver enzyme elevations; and cardiovascular consequences of CGRP inhibition, including effects on blood pressure, heart rate, or other cardiovascular parameters.

Subcutaneous TEV-48125 has generally been well tolerated over the ranges of doses evaluated (single doses of 0.2 to 2000 mg in healthy adults, multiple doses of 30 to 300 mg in healthy adults, and multiple doses of 225 to 900 mg in migraine patients). The most common TEAEs were mild to moderate transient general administration site disorders/reactions. Other commonly reported TEAEs were headache, back pain, and upper respiratory tract infection.

Based on the results from two phase 2b trials (Trials LBR-101-021 and LBR-101-022), in patients with CM, the mean change in headache hours relative to baseline for each TEV-48125 dose group showed a statistically significant reduction in headache hours compared to the placebo group at 3 months (primary endpoint) and reductions also at 1 and 2 months. In patients with EM, the mean change in migraine days relative to baseline for each TEV-48125 dose group showed a statistically significant reduction in migraine days compared to the placebo group at 3 months (primary endpoint) and improvement at 1 and 2 months. Furthermore, results for several secondary/exploratory endpoints also showed TEV-48125 to be superior to placebo.

Based on the above safety profile and the demonstrated efficacy of SC TEV-48125, the benefits of TEV-48125 are expected to outweigh the risks.

Detailed information is presented in the Investigator's Brochure.

2 Trial Rational and Objectives

2.1 Trial Rationale

It has been recommended that preventive treatment of migraine should be continued for 3 to 6 months if no AEs occur[11]. Therefore, even after 6 months have passed since the start of treatment, administration of preventive medication is likely to be continued until migraine is well controlled. Considering the potential long-term use of TEV-48125 in clinical practice, it is considered necessary to accumulate long-term safety data. Based on the International Council for Harmonisation (ICH) E1 Guidelines,[14] data from 100 Japanese patients treated with TEV-48125 for 1 year is needed to evaluate the long-term safety of the drug in Japanese patients.

Nonclinical studies of TEV-48125 required for the conduct of this trial have been completed. The pharmacokinetics and tolerability of TEV-48125 (IV doses ranging from 0.2 to 2000 mg and SC doses of 225, 675, and 900 mg) have been well-characterized in the phase 1 trials. Furthermore, the safety and effectiveness of TEV-48125 has been demonstrated in a randomized, double-blind, placebo controlled phase 2b trial (Trial LBR-101-021) of 2 SC dosing regimens of TEV-48125 (monthly TEV-48125 at 900 mg or TEV-48125 at 675 mg followed by monthly TEV-48125 at 225 mg) in patients with CM and a randomized, double-blind, placebo-controlled phase 2b trial (Trial LBR-101-022) of 2 SC dosing regimens of TEV-48125 (monthly TEV-48125 at 675 or 225 mg) in patients with EM. Based on these results, 2 multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050) and a long-term trial (Trial TV48125-CNS-30051) are ongoing ahead of this trial.

The results of a phase 1 single-dose trial (Trial TV48125-PK-10078) in healthy Japanese and Caucasian subjects have demonstrated similarities in the safety profile of TEV-48125 between the 2 populations, and Japanese patients are enrolled in ongoing multinational phase 3 trials (Trials TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051), which began ahead of this trial. However, it might be difficult to evaluate the long-term safety of TEV-48125 in Japanese patients sufficiently based only on the data from a multinational phase 3 long-term trial (Trial TV48125-CNS-30051) in which less than 100 Japanese patients are expected to complete a 1-year treatment at the same doses and regimens as those specified for phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) that are to be conducted in parallel with this trial. Therefore, it is considered necessary to conduct this trial.

In this trial, in addition to the assessments of long-term safety and tolerability, ADAs to TEV-48125 at a time point where plasma TEV-48125 concentrations are considered to be sufficiently decreased will be measured during an observation period, in which ADA measurements and safety data collection will be conducted in subjects who have completed or discontinued either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002). Given that TEV-48125, an antibody drug conjugate, may work as an antigen and induce ADA production, it is planned to evaluate its immunogenicity and effects of ADAs on the pharmacokinetics, efficacy, and safety of TEV-48125 (ADA assessment).

2.2 Rationale for DNA Storage

In this trial, deoxyribonucleic acid (DNA) samples will be stored on a voluntary basis. Only trial sites that have agreed in advance to collect samples for DNA storage will collect the samples from subjects who have provided written informed consent to the storage of their DNA samples. Concerning collecting DNA samples and storing them during the trial period, the Ministry of Health, Labour and Welfare states in Q&A[15] in "Clinical trials based on pharmacogenomics" (Notification No. 0930007 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau issued on 30 Sep 2008) that samples for genomic/genetic analysis related to the evaluation of an investigational product (eg, pharmacokinetic, efficacy, and safety evaluation) may be collected from subjects during a clinical trial 1) if the target and time of genomic/genetic analysis have been determined when a clinical trial is conducted, or 2) if the target and time of genomic/genetic analysis have not yet been determined when a clinical trial is conducted but there is a plan to perform such analysis in the future to further characterize the investigational product.

In view of the above, it is considered acceptable to store DNA samples for future exploration of possible relationships between treatment response to TEV-48125 and variations of DNA characteristics (eg, genetic polymorphism).

Because subjects rolling over from the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) have already been requested consent for DNA storage, this trial will handle only newly enrolled subjects as candidate subjects for DNA storage.

2.3 Dosing Rationale

TEV-48125 is a preparation for SC injection. Given that a preventive drug needs to be administered for at least 3 to 6 months to prevent migraine attacks, SC administration, an easier dosing modality compared with IV administration, was selected for the convenience of use.

This trial will be conducted to evaluate the long-term safety and tolerability of TEV-48125 given in accordance with the same regimens as those in the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) which are conducted in patients with CM and EM, respectively, in parallel with this trial. Similarly to the dose regimens in the phase 2b/3 trials, TEV-48125 will be administered in this trial subcutaneously at 225 mg once monthly (except for a loading dose of 675 mg for CM patients) or at 675 mg once every 3 months. The dose regimens in each phase 2b/3 trial were selected based on phase 2b trials (Trials LBR-101-021 and LBR-101-022) conducted to evaluate the safety, efficacy, and dose regimens of TEV-48125 primarily in patients with migraine. The doses and dosing regimens used in phase 2b trials were selected based on the result that the 225-mg dose of TEV-48125 was considered the lowest effective dose as demonstrated in nonclinical studies and that the safety of TEV-48125 was confirmed at doses ranging from approximately 225 to 900 mg in phase 1 trials.

In a phase 2b trial in CM patients (Trial LBR-101-021), 2 regimens of 225 mg once monthly (except for a loading dose of 675 mg) and 900 mg once monthly were found to be effective and well tolerated. Both TEV-48125 dose groups showed improvement compared to the placebo group from Month 1, and the difference from placebo group for each TEV-48125 dose group was similar.

In a phase 2b trial in EM patients (Trial LBR-101-022), 2 regimens of 225 or 675 mg once monthly were found to be effective and well tolerated. Both TEV-48125 dose groups showed improvement compared to the placebo group from Month 1, and the difference from placebo group for each TEV-48125 dose group was similar. Based on these findings, the lower dose of TEV-48125 used in these phase 2b trials (Trials LBR-101-021 and LBR-101-022) was considered appropriate for both CM and EM patients in

the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) conducted in parallel with this trial. In the lower dose group in the phase 2b trial in CM patients (Trial LBR-101-021), a loading dose of 675 mg was used despite the lowest effective dose of 225 mg. As it is considered best practice to provide appropriate preventive treatment to CM patients at an early stage, the phase 2b/3 trial (Trial 406-102-00001) conducted in parallel with this trial will also use a loading dose of 675 mg as in the phase 2b trial (Trial LBR-101-021) to facilitate a rapid onset of effect. The phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) conducted in parallel with this trial will have a TEV-48125 675 mg group (dosing once every 3 months) to determine how different doses and dosing regimens may affect the efficacy of TEV-48125 in Japanese patients. This trial will also evaluate the safety, tolerability, and efficacy of TEV-48125 in subjects receiving the drug once every 3 months at a dose of 675 mg.

2.4 Rationale for Treatment Period

The duration of treatment will be 1 year in accordance with the ICH E1 Guideline.[14]

2.5 Trial Objective

To evaluate the long-term safety and tolerability of SC administration of TEV-48125 (at 225 mg once monthly [except for a loading dose of 675 mg in CM patients] or at 675 mg every 3 months) as preventive treatment for CM or 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 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 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
- 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.

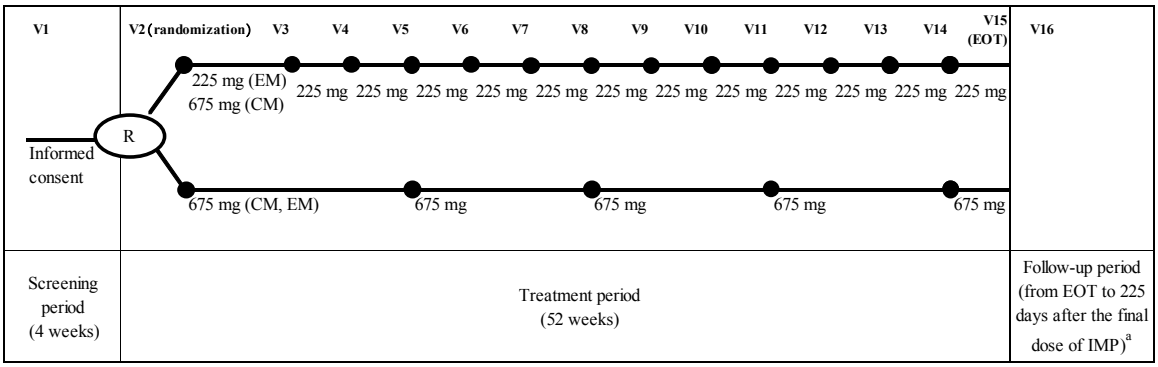


Figure 3.1-1 Trial Design Schematic

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.[16] 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.

3.3.2 Subject Selection and Numbering

After informed consent is obtained, subjects will be assigned a unique subject identification number (site number [3 digits] + S + subject number [5-digit in-site serial number]). The site number (3 digits) will be designated by the sponsor. The subject number (5-digit in-site serial number) will be given at each trial site in the chronological

order informed consent is obtained in, starting at 30001. Following screening, subjects who fail to meet the eligibility criteria will be handled as screen failures. Trial sites will prepare and retain a list of all consented subjects and their subject identification numbers.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent will be freely obtained from all subjects (or legally acceptable representative, etc, if the subject is a minor). Consent will be documented on a written informed consent form (ICF). The written information for subjects and ICF will be approved by the same institutional review board or independent ethics committee/ethics committee (IRB/IEC/EC) that approves this protocol.

Each information for subjects and ICF will comply with the ICH (International Conference on Harmonisation) Good Clinical Practice (GCP) Guideline[17] and local regulatory requirements. The principal investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB/IEC/EC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions, the IRB- or IEC/EC-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee who gave the explanation), as well as by any other parties required by the IRB/IEC/EC. The subject (or legally acceptable representative, etc, if the subject is a minor) will receive the written information for subjects and a copy of the signed ICF; the original shall be kept on file by the investigator.

Subjects may be asked to sign additional ICFs if the protocol is amended to significantly add or change procedures.

For DNA storage, written informed consent will be freely obtained from subjects (or legally acceptable representative, etc, if the subject is a minor) using a separate written information for subjects, by following the above-mentioned procedure. DNA samples

will be stored on a voluntary basis, and subject's refusal to participate in DNA storage will not affect their participation in the main trial.

If a potential subject is a minor, written informed consent will be freely obtained from his or her legally acceptable representative, as applicable for local laws. If the investigator decides that the potential subject is able to understand the explanation of the trial, however, the potential subject will be given an explanation appropriate to his or her ability to understand and then sign and date the ICF by himself or herself.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1. These criteria will not apply to subjects enrolled for ADA assessment only.

Table 3.4.2-1 Inclusion Criteria

1	Males or females age 18 to 70 years, inclusive, at time of informed consent
2	Patient with migraine onset at ≤ 50 years of age
3	Patient signs the informed consent document before start of the trial
4	Patient has a history of migraine (according to The International Classification of Headache Disorders, third edition [beta version] [ICHD-3 beta] criteria [Classification Committee of the International Headache Society 2013]) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 beta diagnosis) for ≥ 12 months prior to giving informed consent
5	Patient fulfills all the following criteria for EM or CM in baseline information collected during the 28-day screening period: [EM] • Headache occurring on ≥ 4 and ≤ 14 days • Fulfilling any of the criteria for migraine listed below on ≥ 4 days: [CM] • Headache occurring on ≥ 15 days • Fulfilling any of the criteria for migraine listed below on ≥ 8 days: Criteria for migraine • ICHD-3 beta diagnostic criteria C and D for 1.1 Migraine without aura (see Appendix 3) • ICHD-3 beta diagnostic criteria B and C for 1.2 Migraine with aura (see Appendix 3) • Probable migraine (a migraine subtype where only 1 migraine criterion is missing) • The patient used a triptan or ergot derivative to treat an established headache.
6	Not using preventive migraine medications (prohibited or restricted medications, see Table 4.1.1-1 and Table 4.1.2-1) for migraine or other medical conditions (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medication (restricted medications, see Table 4.1.2-1) for migraine or other medical condition (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent.
7	Body mass index (BMI) of 17.5 to 37.5 and a total weight between 35.0 and 120.0 kg, inclusive
8	The patient demonstrates compliance with the electronic headache diary during the screening period by entry of headache data on a minimum of 24 of 28 days (≥ 85% diary compliance) and the entered data is judged appropriate by the investigator.
9	The patient is willing and able to comply with trial restrictions and to remain at the trial site for the required duration as specified in this protocol.

[Rationales for inclusion criteria]
1, 2, and 9: These criteria are set to appropriately evaluate efficacy and safety.
3: This criterion is set to ensure the conduct of the trial is ethically appropriate.
4 and 5: These criteria are set to identify patients with EM or CM.
6: This criterion is set to appropriately evaluate efficacy. Since the guidelines developed by the Headache Consortium[4,18] recommend preventive medication for all CM and EM patients having frequent headache and severe impairment, the use of up to 2 preventive medications is permitted during the trial.
7: This criterion is set to ensure appropriate administration of the IMP and appropriate evaluation of efficacy and safety.
8: This criterion is set to appropriately evaluate efficacy.

3.4.3 Exclusion Criteria

Subjects will be excluded if they fall under any of the exclusion criteria in Table 3.4.3-1. These criteria will not apply to subjects enrolled for ADA assessment only.

Table 3.4.3-1 Exclusion Criteria

1	Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator
2	Evidence or medical history of clinically significant psychiatric issues, including any suicide attempt in the past, or suicidal ideation with a specific plan in the past 2 years
3	History of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], or peripheral extremity ischemia, or other ischemic event) or thromboembolic events (arterial or venous thrombotic or embolic events), such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism
4	Known infection or history of human immunodeficiency virus (HIV), tuberculosis, or hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
5	Past or current history of cancer in the past 5 years, except for appropriately treated skin carcinoma other than malignant melanoma
6	History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
7	Participation in a clinical trial of another drug or medical device within 2 months or 5 half-lives of the other drug, whichever is longer, prior to IMP administration in the present trial
8	Any prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG334, ALD304, LY2951742, or TEV-48125)
9	Any finding in the screening or baseline 12-lead ECG considered clinically significant in the judgment of the investigator
10	Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including in chemistry, hematology, coagulation, and urinalysis test values
11	ALT, AST, and ALP more than 1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law at screening
12	Serum creatinine more than 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease at screening
13	History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years

Table 3.4.3-1 Exclusion Criteria	
14	Female patient who is nursing at the time informed consent is obtained, or who tests positive in pregnancy test at screening or baseline
15	Sexually active males or women of childbearing potential (WOCBP) who do not agree to practice 2 different methods of birth control together with their partner throughout the trial period and for 225 days after the final dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Note) Nonchildbearing potential is defined as male and female subjects who are surgically sterile (ie, male subjects who have undergone bilateral orchidectomy and female subjects who have undergone bilateral oophorectomy and/or hysterectomy) and female subjects who have been postmenopausal (at least 12 months since last menses and follicle-stimulating hormone [FSH] above 35 U/L).
16	The patient cannot participate or successfully complete the trial for other reasons in the opinion of the investigator.

Screen failure subjects who fall under the exclusion criterion 7, 14, or 15 during the screening period (including V1/Screening) may be rescreened only once if the characteristics of the exclusion criterion 7, 14, or 15 have changed after the assessment as screen failures. In the event that a subject is rescreened, a new ICF must be signed and a new subject identification number must be assigned prior to the rescreening. However, if it cannot be confirmed that a subject meets all the inclusion criteria and does not fall under any of the exclusion criteria at V2/Baseline, the subject will not be eligible for rescreening.

[Rationales for exclusion criteria]
1 through 5, 7, 8, 13, and 16: These criteria are set to appropriately evaluate efficacy and safety.
6 and 9 to 12: These criteria are set to appropriately evaluate safety.
14 and 15: These criteria are set because the safety of administering IMP in pregnant or nursing females has not been established.

3.5 Endpoints

Section 3.5.1 Safety Endpoints and Section 3.5.2 Efficacy Endpoints apply only to subjects who are to receive the IMP.

3.5.1 Safety Endpoints

The safety endpoints for this trial are as follows:

- AEs
- Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis)
- 12-Lead ECGs
- Physical examination

- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- Weight
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments (including severity)
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

3.5.2 Efficacy Endpoints

The efficacy endpoints for this trial are as follows:

- Number of migraine days
- Number of headache days of at least moderate severity
- Number of headache days of any severity
- Number of days with use of any acute headache medications
- Number of subjects discontinuing concomitant preventive migraine medications during the treatment period
- Number of days with nausea or vomiting
- Number of days with photophobia or phonophobia
- 6-Item Headache Impact Test (HIT-6) (for subjects with CM only)
- Migraine Disability Assessment (MIDAS) (for subjects with EM only)
- Migraine-Specific Quality of Life (MSQOL)
- EuroQol-5 Dimension, 5 response level version (EQ-5D-5L)
- Patient Global Impression of Change (PGIC)
- 2-Item Patient Health Questionnaire (PHQ-2) and 9-Item Patient Health Questionnaire (PHQ-9)
- Work Productivity and Activity Impairment (WPAI)

3.5.3 Pharmacokinetic Endpoint

The pharmacokinetic endpoint for this trial is as follows:

- Plasma TEV-48125 concentrations

3.5.4 Immunogenicity Endpoint

The immunogenicity endpoint for this trial is as follows:

- Incidence of serum anti-TEV-48125 antibodies

3.6 Measures to Minimize/Avoid Bias

This is a randomized, open-label trial. Subjects with CM or EM will be randomly assigned to treatment groups for CM or EM, respectively. Details are presented in the Procedure for Subject Randomization Code.

3.7 Trial Procedures

3.7.1 Schedule of Assessments

Trial assessment time points for subjects receiving IMP are summarized in Table 3.7.1-1.

Section 3.7.1.1, Screening Period, through Section 3.7.1.4, Unscheduled Visits, will apply only to subjects receiving IMP. For subjects enrolled for ADA assessment only, refer to Section 3.7.1.5, Schedule for Subjects Enrolled for ADA Assessment Only.

Table 3.7.1-1 Schedule of Assessments for Subjects Receiving IMP

Procedures and Assessments	Period	Screening Period	Treatment Period															Follow-up Period
	Visit	V1/ Screening	V2/ Baseline	V3/ Month 1	V4/ Month 2	V5/ Month 3	V6/ Month 4	V7/ Month 5	V8/ Month 6	V9/ Month 7	V10/ Month 8	V11/ Month 9	V12/ Month 10	V13/ Month 11	V14/ Month 12	V15/ End of treatment	Withdrawal	V16/Follow up
	Study Day	Day -28	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		Day 562
	Acceptable window	-5	-	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	Day of withdrawal decision + 7	±15
Informed consent		X[a]																
Informed consent to DNA storage (voluntary)		X																
Demographics		X																
Eligibility assessment		X	X															
Randomization			X															
IMP administration			X	X[o]	X[o]	X	X[o]	X[o]	X	X[o]	X[o]	X	X[o]	X[o]	X			
Injection site assessments[b]			X	X[o]	X[o]	X	X[o]	X[o]	X	X[o]	X[o]	X	X[o]	X[o]	X			
Physical examination		X	X	X	X	X		X	X					X	X	X	X	X
Height		X																
Weight		X	X	X	X	X		X	X					X	X	X	X	X
12-Lead ECG[c]		X	X													X	X	
Vital signs[c] (systolic/diastolic blood pressure, pulse rate, temperature, respiratory rate)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis)		X	X		X		X		X		X		X		X	X	X	
Serum HCG test[d]		X																
Urine HCG test[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FSH test[e]		X																
Adverse events[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Preventive migraine medication inquiry			X															
Medication and therapy inquiry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eC-SSRS[g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3.7.1-1 Schedule of Assessments for Subjects Receiving IMP

Procedures and Assessments	Period	Screening Period	Treatment Period														Follow-up Period
	Visit	V1/ Screening	V2/ Baseline	V3/ Month 1	V4/ Month 2	V5/ Month 3	V6/ Month 4	V7/ Month 5	V8/ Month 6	V9/ Month 7	V10/ Month 8	V11/ Month 9	V12/ Month 10	V13/ Month 11	V14/ Month 12	V15/ End of treatment	Withdrawal	V16/Follow up
	Study Day	Day -28	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	Day 225	Day 253	Day 281	Day 309	Day 337	Day 365		Day 562
	Acceptable window	-5	-	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	Day of withdrawal decision + 7	±15
Provide electronic headache diary device[h]		X						X						X				
Complete electronic headache diary entries[i]		X	—	—	—	X		X	— X					X	— X		X[p]	
Review electronic headache diary			X	X	X	X			X						X		X[p]	
Return electronic headache diary device						X			X						X		X[p]	
Blood samples for plasma drug concentration			X			X			X						X	X	X	X
Blood samples for serum ADA assessment[j]			X			X			X						X	X	X	X
Blood samples for pharmacogenomic analysis[k]			X															
Blood/urine samples for biomarker assessment			X						X						X		X	X
HIT-6[l]			X						X						X		X	
MIDAS questionnaire[m]			X						X						X		X	
PHQ-2/PHQ-9[n]			X						X						X		X	
MSQOL questionnaire			X						X						X		X	
EQ-5D-5L questionnaire			X						X						X		X	
PGIC scale				X		X			X			X			X		X	
WPAI questionnaire			X						X						X		X	

HCG = serum human chorionic gonadotropin.

[a] Informed consent can be obtained prior to the day of V1/Screening.

[b] Injection site assessments will be performed immediately and 1 hour postdose. If a subject has severe injection site erythema, induration, and/or ecchymosis, and/or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of IMP administration, the subject will be reassessed hourly thereafter until the reaction/pain is of moderate or less severity.

[c] Procedure will be performed before other assessments (blood draws and administration of questionnaires).

[d] Women of childbearing potential only.

[e] Women at least 12 months postmenopausal only.

[f] Inquiries about AEs will be made at every visit. At V2/Baseline through V14/Month 12, inquiries about AEs will be made before and after IMP administration. Postdose inquiries will be made before the subject leaves the trial site.

[g] The eC-SSRS Baseline/Screening version will be completed at V2/Baseline, and the eC-SSRS Since Last Visit version will be completed at all other visits.

[h] Eligible subjects will be given an electronic headache diary device (eDiary) and will be trained in its use and compliance requirements at V1/Screening.

[i] Each day from V1/Screening until the day before V2/Baseline, from V2/Baseline until the day before V5/Month 3, from V7/Month 5 until the day before V8/Month 6, and from V13/Month 11 until the day before V14/Month 12, subjects will complete electronic headache diary entries about the previous day.

[j] Blood samples for serum ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).

[k] A single blood sample for pharmacogenomic analysis will be collected at any visit during the period from V2/Baseline to V16/Follow-up from subjects who consent to DNA storage. A separate informed consent form for DNA storage must be signed by the subject.

[l] The HIT-6 will only be administered to subjects with CM.

[m] The MIDAS questionnaire will only be administered to subjects with EM.

[n] Subjects will respond first to the PHQ-2. They will respond to questions 3 through 9 (unique questions) of the PHQ-9 only if PHQ-2 is positive.

[o] To be performed in subjects with CM or EM in the TEV-48125 225 mg/1 month group only.

[p] Applicable cases only.

3.7.1.1 Screening Period

The screening period begins on the day of informed consent and ends on the day before V2/Baseline.

An appropriately signed and dated ICF will be obtained before screening procedures commence. After informed consent is obtained, the investigator (or designee) will promptly enter the subject's information in the IRT and obtain a subject identification number as described in Section 3.3.2, Subject Selection and Numbering.

The following information will be recorded on the case report form (CRF):

- Informed consent
  - Date of informed consent
  - Subject identification number

For headache information on each day from V1/Screening through the day before V2/Baseline, subjects will enter headache information about the previous day into the electronic headache diary. The data used for inclusion criterion 5 will be those from the electronic headache diary within the last 28 days prior to V2/Baseline.

12-Lead ECGs and clinical laboratory values measured by the central laboratory, which cannot be assessed at V1/Screening, should be checked against inclusion/exclusion criteria soon after they become available to determine the subject's eligibility.

3.7.1.1.1 Visit 1/Screening (Day −28; Acceptable Window: −5 Days)

V1/Screening will take place 28 days before V2/Baseline. In order to determine the subject's eligibility, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Result of eligibility assessment
- Demographics
  - Date of investigation
  - Birth date, age, and sex (at the time of informed consent)
  - Childbearing potential (Reason for nonchildbearing potential, or contraceptive methods)
  - Race, ethnicity, and country
  - Medical history and complications (at the time of informed consent)
  - Medical history for migraine
  - History of preventive migraine medications (including topiramate and onabotulinumtoxin A) (within 2 years before the start of IMP administration [if discontinued before consent, its reason])

  - History of medications or therapies other than preventive migraine medications (within 5 months before the start of IMP administration)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling)
- 12-lead ECGs (should precede blood sampling)
- Physical examination
- Height and weight (BMI will be calculated using height and weight at V1/Screening)
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Serum human chorionic gonadotropin (HCG) test (women of childbearing potential [WOCBP] only)
  - Follicle-stimulating hormone (FSH) test (women at least 12 months postmenopausal only)
- Electronic headache diary (subjects will be given an electronic headache diary device [eDiary], trained in its use, and given an explanation on the compliance requirements)
- AEs

3.7.1.2 Treatment Period

The treatment period begins at V2/Baseline and ends at V15/End of treatment or the time of withdrawal. For headache information on each day from V2/Baseline until the day before V5/Month 3, from V7/Month 5 until the day before V8/Month 6, and from V13/Month 11 until the day before V14//Month 12, subjects will enter headache information about the previous day into the electronic headache diary device.

3.7.1.2.1 Baseline

3.7.1.2.1.1 Visit 2/Baseline (Day 1)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF. The investigator will confirm that the subject meets all the inclusion criteria and does not fall under any of the exclusion criteria.

Trial personnel responsible for administration of injections will subcutaneously administer the IMP assigned by the procedure presented in Section 3.7.1.2.1.2, Randomization, to the subject.

If it cannot be confirmed that a subject meets all the inclusion criteria and does not fall under any of the exclusion criteria at V2/Baseline, the subject will not be eligible for rescreening.

- Visit date
- Result of eligibility assessment

- Use of preventive migraine medications
- Result of migraine diagnosis
- Randomization
  - Date of randomization
  - Treatment group
- Electronic headache diary
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- 12-lead ECGs (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood and urine sampling for biomarker assessment
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline to V16/Follow-up)
- HIT-6 (only subjects with CM)
- MIDAS questionnaire (only subjects with EM)
- PHQ-2/PHQ-9 (Subjects will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHW-9 only if PHQ-2 is positive.)
- MSQOL questionnaire
- EQ-5D-5L questionnaire
- WPAI questionnaire
- eC-SSRS (Baseline/Screening version)
- History of medications and therapies (within 5 months before the start of IMP administration)
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 675 mg/3 months group and subjects with CM in the TEV-48125 225 mg/1 month group will subcutaneously receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL), and subjects with EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based

on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose adverse events (occurring before the subject leaves the trial site)

3.7.1.2.1.2 Randomization

Prior to IMP administration, the investigator will confirm that the subject meets all the inclusion criteria and does not fall under any of the exclusion criteria. Then, the investigator (or designee) will enter subject information in the IRT.

Subjects with CM or EM will be randomly assigned to either of the following 2 treatment groups for CM or EM, respectively:

[CM]

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

[EM]

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

3.7.1.2.2 Visit 3/Month 1 (Day 29; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Electronic headache diary
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- PGIC scale
- eC-SSRS (Since Last Visit version)

- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.3 Visit 4/Month 2 (Day 57; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Electronic headache diary
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the

following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.4 Visit 5/Month 3 (Day 85; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Electronic headache diary (Subjects will return the eDiary)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- PGIC scale
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 675 mg/3 months group will subcutaneously receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL), and subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.5 Visit 6/Month 4 (Day 113; Acceptable Window: ± 5 Days), Visit 10/Month 8 (Day 225; Acceptable Window: ± 5 Days), and Visit 12/Month 10 (Day 281; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.6 Visit 7/Month 5 (Day 141; Acceptable Window: ± 5 Days) and Visit 13/Month 11 (Day 309; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Electronic headache diary (Subjects will be given an eDiary, and will be trained in its use and given an explanation on the compliance requirements again as needed. Subjects will be instructed to enter headache information from the next day.)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.7 Visit 8/Month 6 (Day 169; Acceptable Window: ± 5 Days) and Visit 14/Month 12 (Day 337; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Electronic headache diary (Subjects will return the eDiary.)

- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood and urine sampling for biomarker assessment
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- HIT-6 (for subjects with CM only)
- MIDAS questionnaire (for subjects with EM only)
- PHQ-2/PHQ-9 (Subjects will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHW-9 only if PHQ-2 is positive.)
- MSQOL questionnaire
- EQ-5D-5L questionnaire
- PGIC scale
- WPAI questionnaire
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 675 mg/3 months group will subcutaneously receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL), and subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
- Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)

- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.8 Visit 9/Month 7 (Day 197; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
  - Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.9 Visit 11/Month 9 (Day 253; Acceptable Window: ± 5 Days)

Prior to IMP administration, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- Urine HCG test (WOCBP only)
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)

- PGIC scale
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects with CM or EM in the TEV-48125 675 mg/3 months group will subcutaneously receive 675 mg of TEV-48125 as 3 injections (225 mg/1.5 mL), and subjects with CM or EM in the TEV-48125 225 mg/1 month group will subcutaneously receive 225 mg of TEV-48125 as a single injection (225 mg/1.5 mL). After IMP administration, the following assessments/observations will be performed and recorded on the CRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (ie, erythema, induration, ecchymosis, and pain).

- Conditions of IMP administration
  - Date, time, and injection site of IMP administration
  - If IMP was not administered, its reason
  - Injection site reaction (ie, erythema, induration, ecchymosis, and pain) assessments, including severity (immediately and 1 hour postdose)
- Postdose AEs (occurring before the subject leaves the trial site)

3.7.1.2.10 Visit 15/End of Treatment (Day 365; Acceptable Window: ± 5 Days)

As the final evaluation (V15/End of treatment), the following assessments/tests/observations will be performed. The results of assessments/tests/observations will be recorded on the CRF.

- Visit date
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- 12-lead ECGs (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood sampling for plasma drug concentration determination

- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

3.7.1.2.11 Withdrawal (Acceptable Window: Day of Withdrawal Judgment + 7 Days)

For withdrawals, the following assessments/tests/observations will be performed wherever possible within the acceptable window. The results of assessments/tests/observations will be recorded on the CRF. The day of withdrawal decision is defined as the date when the subject (or legally acceptable representative, etc, if the subject is a minor) submits a request for withdrawal or when the subject's withdrawal is considered necessary by the investigator. Procedures for withdrawal from the trial are described in Section 3.8.3, Individual Subject Discontinuation.

- Visit date
- Completion of Trial
  - Trial completion date/discontinuation date
  - In the case of withdrawal, reason for discontinuation
- Electronic headache diary (Subjects will return the eDiary, if applicable.)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)
- 12-lead ECGs (should precede blood sampling and questionnaires)
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood and urine sampling for biomarker assessment
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- HIT-6 (for subjects with CM only)
- MIDAS questionnaire (for subjects with EM only)
- PHQ-2/PHQ-9 (Subjects will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHW-9 only if PHQ-2 is positive.)

- MSQOL questionnaire
- EQ-5D-5L questionnaire
- PGIC scale
- WPAI questionnaire
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

3.7.1.3 Visit 16/Follow-up (Acceptable Window: ± 15 Days)

At 225 days (± 15 days) after the final dose of IMP, the following assessments/tests/observations will be performed and recorded on the CRF.

- Visit date
- Physical examination
- Weight
- Blood sampling for serum ADA assessment
- Blood and urine sampling for biomarker assessment
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline up to V16/Follow-up)
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

3.7.1.4 Unscheduled Visits

An unscheduled visit may be performed at any time during the trial, at the subject's request or as deemed necessary by the investigator, and assessments/tests/observations will be performed. The date of the unscheduled visit and the results of the assessments/tests/observations, only those performed according to the procedures specified in the protocol, will be recorded on the CRF. Other procedures may be performed at the discretion of the investigator.

3.7.1.5 Schedule for Subjects Enrolled for ADA Assessment Only

An appropriately signed and dated ICF will be obtained at V5/End of treatment or withdrawal in either of the phase 2b/3 trials (Trials 406-102-00001 or 406-102-00002). After informed consent is obtained, the investigator (or designee) will promptly enter the subject's information in the IRT and obtain a subject identification number as described in Section 3.3.2, Subject Selection and Numbering.

The following information will be recorded on the CRF:

- Visit date
- Informed consent
  - Date of informed consent
  - Subject identification number
- Demographics
  - Date of investigation
  - Birth date, age, and sex
  - Race, ethnicity, and country

At 225 days (± 15 days) after the final dose of IMP in either phase 2b/3 trial (Trials 406-102-00001 and 406-102-00002), the following assessments/tests/observations for V16/Follow-up will be performed and recorded on the CRF. Subjects whose V16/Follow-up is scheduled after code breaking of the phase 2b/3 trials and who are found to have been in the placebo group will end their participation in this trial without undergoing V16/Follow-up. The date on which they are informed that they do not need to return to the trial site for V16/Follow-up will be regarded as the end of trial date for these subjects.

- Visit date
- Blood sampling for serum ADA assessment
- Blood sampling for plasma drug concentration determination
- Concomitant medications and therapies
- AEs

3.7.2 Efficacy Assessment

Any efficacy endpoint data will be electronically collected. Data on headache-related efficacy endpoints will be collected using eDiary, and data on overall functional assessments, physical assessments, and other relevant assessments (Section 3.7.2.2 through Section 3.7.2.8) will be collected using Electronic Patient-Reported Outcomes (ePRO).

3.7.2.1 Electronic Headache Diary

Headache-related efficacy endpoints will be derived from headache variables collected using an eDiary. Eligible subjects will receive comprehensive training from trial personnel on the use of the eDiary at V1/Screening. On each day, the subject will be asked to enter headache data in the electronic headache diary for the previous 24-hour period. Subjects who report headache on the previous day will answer questions about

the headache (ie, occurrence of headache, duration of headache, maximum severity of headache, presence/absence of associated symptoms, and use of acute headache medications).

Headache data for the preceding day should be entered into the electronic headache diary by the data entry time limit of 2 days (48 hours). If this time limit is exceeded, the subject will not be able to enter headache information for the applicable day, and it will be considered a missing day. If a subject has not entered the headache data by 8 PM of the next day, the subject will be reminded to enter the data.

Overall headache duration will be recorded numerically, in hours, as well as number of hours with headache of at least moderate severity.

If headache is reported, then headache severity will be subjectively rated by the subject as follows:

- Mild headache
- Moderate headache
- Severe headache

Subjects will also record the presence or absence of photophobia, phonophobia, nausea, or vomiting, and the status of use of any acute headache medications.

3.7.2.2 Six-Item Headache Impact Test (Subjects With CM Only)

The investigator will instruct subjects to complete the HIT-6 to assess the impact of headache on their social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Only subjects with CM will be required to complete the HIT-6.

3.7.2.3 Migraine Disability Assessment Questionnaire (Subjects With EM Only)

The investigator will instruct subjects to complete the MIDAS questionnaire to assess the degree of headache-related disability based on lost days of activity in 3 domains (work, household work, and nonwork) over the last 3 months. The MIDAS questionnaire is a 5-item instrument. The total of the scores of the first 5 questions is used for grading the level of disability, with scores of 0 to 5, 6 to 10, 11 to 20, and ≥ 21 interpreted as disability grades I (little or no disability), II (mild disability), III (moderate disability), and IV (severe disability), respectively. Only subjects with EM will be required to complete the MIDAS questionnaire.

3.7.2.4 Two-Item Patient Health Questionnaire/Nine-Item Patient Health Questionnaire

The investigator will instruct subjects to complete PHQ-2 and PHQ-9 for detection and monitoring depression, anxiety, and somatization during the last 2 weeks. The PHQ is a 9-item questionnaire with each item corresponding to 1 criterion of the Diagnostic and Statistical Manual for Mental Disorders fourth edition diagnostic criteria for major depressive disorder. Each of the items is scored on a scale of 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day) based on the frequency of symptoms during the past 2 weeks. The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression and consists of the first 2 questions from the PHQ-9.

All subjects will complete the PHQ-2. If the PHQ-2 is positive (ie, a score of ≥ 3), subjects will complete questions 3 through 9 (unique questions) of the PHQ-9.

3.7.2.5 Migraine-Specific Quality of Life Questionnaire

The investigator will instruct subjects to complete the MSQOL questionnaire to assess the impact of migraine and migraine treatment on their quality of life during the past 4 weeks. The MSQOL measures the degree to which performance of normal activities is limited by migraine (Role Function-Restrictive domain comprising 7 items), the degree to which performance of normal activities is prevented by migraine (Role Function-Preventive domain comprising 4 items), and the emotional effects of migraine (Emotional Function domain comprising 3 items). Scores range from 0 to 100, with higher scores indicating better health-related quality of life.

3.7.2.6 EuroQol-5 Dimension, 5 Response Level Version Questionnaire

The investigator will instruct subjects to complete the EQ-5D-5L questionnaire to assess their overall state of health on the day of assessment. The EQ-5D-5L questionnaire consists of 2 parts. In Part 1, subjects rate their health state in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, using a scale of 1 to 5 where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. In Part 2, subjects rate their health state on a 100-mm visual analog scale; a rating of 0 represents the worst imaginable health state, and a rating of 100 represents the best imaginable health state.

3.7.2.7 Patient Global Impression of Change Scale

The investigator will instruct subjects to complete the PGIC scale to assess overall change in the severity of illness following treatment. Subjects will rate how they describe the change (if any) that their migraine/headaches have had in their general quality of life and health status since beginning the treatment in this trial on a 7-point

scale where 1 = no change (or it got worse); 2 = almost the same, hardly any change at all; 3 = a little better, but no noticeable change; 4 = somewhat better, but the change has not made any real difference; 5 = moderately better, and a slight but noticeable change; 6 = better, and a definite improvement that has made a real and worthwhile difference; and 7 = a great deal better, and a considerable improvement that has made all the difference.

3.7.2.8 Work Productivity and Activity Impairment Questionnaire

The investigator will instruct subjects to complete the generic version of the WPAI questionnaire to assess the overall effect of health on productivity at work and daily activities during the past 7 days prior to the assessment day. The investigator will also instruct subjects to complete the specific health problems version of the WPAI questionnaire, which allows investigators to attribute productivity and activity impairment issues to specific health conditions. After the employment status of a respondent is identified, 3 open-ended questions are asked concerning 1) hours absent from work due to health problems (or specific condition), 2) hours absent from work due to other reasons, and 3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, one concerning productivity at work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment).

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed for the parameters listed in Table 3.7.3.2-1. The total volume of blood to be collected for each subject in this trial is approximately 109.2 mL.

All clinical laboratory tests in this trial, excluding urine HCG tests, will be performed using the central laboratory selected by the sponsor. The investigator will confirm the eligibility of each subject based on clinical laboratory values measured by the central laboratory. Any additional clinical laboratory tests, if required besides those performed at scheduled time points for blood/urine collection for reasons such as AEs, will also be performed by the protocol-specified central laboratory. The collection, treatment, storage,

and shipment of samples will be performed as described in a separate operational procedure.

For WOCBP, a serum HCG test will be performed at V1/Screening and a urine HCG test will be performed at V2/Baseline and all subsequent visits. If a urine HCG test performed at V3/Month 1 or any later visit is positive, the investigator will follow up with a confirmatory serum HCG test. For women who have been postmenopausal for at least 12 months since last menses, an FSH test will be performed at V1/Screening.

The central laboratory will report clinical laboratory test results to the investigator. The investigator will confirm the results promptly, and date and sign the clinical laboratory test results report as an official document. The date and time of blood/urine collection and whether during menses or not will be recorded on the CRF. The results of clinical laboratory tests, excluding urine HCG tests, will be directly reported from the central laboratory to the sponsor via electronic file transfer; therefore, recording of the results on the CRF is not needed. The results of urine HCG tests will be recorded on the CRF.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology Hemoglobin Hematocrit Erythrocytes count Erythrocyte indices • Mean corpuscular hemoglobin concentration • Mean corpuscular volume • Erythrocytes distribution width Leukocytes count and differential count (absolute values and percentages) • Neutrophils • Lymphocytes • Eosinophils • Monocytes • Basophils Platelet count Urinalysis Appearance Color Occult blood Glucose Microscopic tests (high-power field) • Bacteria • Leukocytes count • Erythrocytes count • Casts • Crystals pH Protein Specific gravity Albumin Ketones Leukocyte esterase Nitrite Direct bilirubin	Chemistry ALP ALT AST Total bilirubin Direct bilirubin Indirect bilirubin (calculated) Urea nitrogen Calcium Creatinine Gamma glutamyl transferase (GGT) Glucose Lactate dehydrogenase Potassium Total protein Sodium Phosphorus Chloride Carbon dioxide Magnesium Albumin Creatine phosphokinase Coagulation Prothrombin time Partial thromboplastin time International normalization ratio (INR) Additional tests Serum/urine HCG test for WOCBP FSH test for women who have been postmenopausal for at least 12 months since last menses

3.7.3.3 Physical Examination

For physical examination, the following organ systems will be assessed/observed: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Physical examinations of individual subjects will be performed by the same site personnel to the extent possible. On the CRF, the date and results of assessments will be recorded at V1/Screening, and only the date of assessments will be recorded at V2/Baseline and subsequent visits. Any clinically significant physical finding that is not observed at V1/Screening but at

V2/Baseline or any later visit will be considered an AE, recorded on the source documents and CRFs, and monitored until its outcome has been sufficiently evaluated.

3.7.3.4 Height and Weight

Weight will be measured while minimizing fluctuations associated with clothing. Date of measurement, height (up to one decimal place; cm), and weight (up to one decimal place; kg) will be recorded on the CRF. Any height/weight measured up to more than one decimal place will be rounded up to one decimal place.

3.7.3.5 Vital Signs

As vital signs, systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate will be measured before other assessments (blood draws and questionnaires). Before pulse rate and blood pressure are measured, the subject must be in a supine or semi-standing/sitting position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given subject (however, if it is difficult to use the same position and arm due to occurrence of an AE, use of a different position or arm is acceptable). Date of measurement, position, location, pulse rate (integer; beats/min), systolic and diastolic blood pressures (integer; mmHg), temperature (up to one decimal place; ºC), and respiratory rate (integer; breaths/min) will be recorded on the CRF. Any vital sign value, excluding temperature, which is measured up to one decimal place or more will be rounded to the closest whole number, and any temperature value measured up to more than one decimal place will be rounded to one decimal place.

3.7.3.6 Twelve-lead Electrocardiography

Using 12-lead ECG equipment provided by the central laboratory selected by the sponsor, ECGs will be conducted before other assessments (blood draws and questionnaires). The ECGs should be performed after the subject has been supine for at least 5 minutes.

Clinical evaluation of ECG results will be performed by the investigator. A qualified physician at the central laboratory selected by the sponsor will interpret ECG results. ECGs will be measured and transmitted in accordance with a separate operational procedure. If clinically significant ECG findings are detected by the investigator, a medical advisor should be consulted for a definitive interpretation. Any unscheduled ECGs must also be transmitted to the designated central laboratory. The central laboratory will report the results of ECGs to the investigator. The investigator will confirm the results promptly, and date and sign the electrocardiogram report as an official document. Date of ECG and the interpretation of the investigator will be recorded on the CRF. The central ECG interpretations and findings will be directly reported from the

central laboratory to the sponsor via electronic file transfer; therefore, recording of the results on the CRF is not needed.

3.7.3.7 Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)

The eC-SSRS will be used to assess the subject's suicidal ideation (severity and intensity) and suicidal behavior.[19] The investigator will ask the subject to complete the eC-SSRS Baseline/Screening version at V2/Baseline and the eC-SSRS Since Last Visit version at all other time points. Any positive findings on the eC-SSRS Baseline/Screening version or the eC-SSRS Since Last Visit version require evaluation by the investigator.

3.7.3.8 Injection Site Reaction Assessments

Injection site reaction assessments will be performed immediately and 1 hour after each IMP administration. The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain, and severity will be graded according to the following criteria. If a subject has severe injection site erythema, induration, and/or ecchymosis and/or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of IMP administration, the subject will be reassessed hourly thereafter until the reaction/pain is of moderate or less severity.

- Injection-site erythema, induration, and ecchymosis will be graded according to measurements:
  absent, 5 to ≤ 50 mm (mild), > 50 to ≤ 100 mm (moderate), and > 100 mm (severe).
  Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
- Injection-site pain will be evaluated according to Table 3.7.3.8-1.

For injection site assessments, the date and time and results of evaluation will be recorded on the CRF, and an injection site reaction (mild, moderate, or severe) is to be reported as an AE. Pain caused by the puncture of the injection needle will be excluded from the assessment, and is not considered to be an AE.

Table 3.7.3.8-1 Severity Grading of Pain for Injection Site Assessments

Grade	Assessments
0	No pain
1	Mild
2	Moderate
3	Severe
4	Worst possible

3.7.3.9 Prior and Concomitant Therapy or Medication

Monitoring will be performed on any prior or concomitant preventive migraine medication (including topiramate and onabotulinumtoxin A) that a subject takes during the period from 2 years before the start of IMP administration to the end of trial date for individual subject (including reasons for discontinuation if any of such medications has been discontinued before informed consent) and any other prior or concomitant medication or therapy that a subject takes during the period from 5 months before the start of IMP administration and up to the end of trial period. For each medication or therapy, the following information will be recorded on the CRF: name, indication, dose, frequency, route of administration, start date, and end date.

3.7.4 Pharmacokinetic/pharmacodynamic/pharmacogenomic Assessments

3.7.4.1 Pharmacokinetics

3.7.4.1.1 Pharmacokinetic Blood Samples

(1) Timing of Blood Sampling

- V2/Baseline (Day 1): Predose
- V5/Month 3 (Day 85; acceptable window: ± 5 days): Predose
- V8/Month 6 (Day 169; acceptable window: ± 5 days): Predose
- V14/Month 12 (Day 337; acceptable window: ± 5 days): Predose
- V15/End of treatment (Day 365; acceptable window: ± 5 days)
- Withdrawal (acceptable window: day of withdrawal decision + 7 days)
- V16/Follow-up (225 days after the final dose of IMP, acceptable window: ± 15 days)

From V2/Baseline through V15/End of treatment, blood will be collected only from newly enrolled subjects who are to be treated with the IMP in this trial. At V16/Follow-up, blood will be collected from subjects enrolled solely for ADA assessment 225 days (acceptable window: ± 15 days, the approximate equivalent of 5 half-lives of TEV-48125) after the final dose of IMP in either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002).

(2) Blood Sampling and Measurement Methods

Blood will be collected at the scheduled time points to obtain pharmacokinetic plasma samples. The central laboratory will collect samples and transport them to the drug concentration measurement facility. Detailed sample handling and shipping instructions are provided in Appendix 1.

The drug concentration measurement facility will measure plasma concentrations of TEV-48125 in subjects treated with TEV-48125, using a validated measurement method.

The drug concentration measurement facility will submit the electronic file of the results of drug concentration measurements to the sponsor.

Blood sampling status (performed or not) and date and time of blood sampling will be recorded on the CRF. The results of measurements will be directly reported from the drug concentration measurement facility to the sponsor; therefore, recording of the results on the CRF is not needed.

(3) Rationale for Timing of Blood Sampling

In order to evaluate effects of ADA on plasma concentrations of TEV-48125, it is planned to collect blood at the same time points as V2/Baseline, V5/Month 3, V8/Month 6, V14/Month 12, V15/End of treatment, withdrawal, and V16/Follow-up, at which ADAs will be measured. Consequently, blood will be collected from each subject at a maximum of 6 time points.

3.7.4.2 Immunogenicity

(1) Timing of Blood Sampling

- V2/Baseline (Day 1): Predose
- V5/Month 3 (Day 85; acceptable window: ± 5 days): Predose
- V8/Month 6 (Day 169; acceptable window: ± 5 days): Predose
- V14/Month 12 (Day 337; acceptable window: ± 5 days): Predose
- V15/End of treatment (Day 365; acceptable window: ± 5 days)
- Withdrawal (acceptable window: day of withdrawal decision + 7 days)
- V16/Follow-up (225 days after the final dose of IMP, acceptable window: ± 15 days)
- Upon observation of any severe hypersensitivity reaction (eg, anaphylaxis)

From V2/Baseline through V15/End of treatment, blood will be collected only from newly enrolled subjects who are to be treated with the IMP in this trial. At V16/Follow-up, blood will be collected from subjects enrolled solely for ADA assessment in order to evaluate the immunogenicity at 225 days (acceptable window: ± 15 days, the approximate equivalent of 5 half-lives of TEV-48125) after the final dose of IMP in either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002).

See Appendix 2 for the clinical criteria for diagnosing anaphylaxis.

(2) Blood Sampling and Measurement Methods

Blood will be collected at the scheduled time points to obtain serum samples for ADA assessments. The central laboratory will collect samples and transport them to the ADA measurement facility. Detailed sample handling and shipping instructions are provided in Appendix 1.

The ADA measurement facility will measure anti-TEV-48125 antibodies in serum samples collected from subjects treated with TEV-48125, using a validated measurement method. The ADA measurement facility will submit the electronic file of the results of ADA measurements to the sponsor.

Blood sampling status (performed or not) and date and time of blood sampling will be recorded on the CRF. The results of measurements will be directly reported from the ADA measurement facility to the sponsor; therefore, recording of the results on the CRF is not needed.

(3) Rationale for Timing of Blood Sampling

It was determined to collect blood at 1 time point before the first dose as baseline; 2 time points, V5/Month 3 and V8/Month 6, with an interval of 3 months, which is longer than the sampling interval evaluated for the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002); and 1 time point, V14/Month 12, with an interval of 6 months. In addition, blood will be collected at 1 time point, V15/End of treatment, which is 28 days after the final dose of IMP in consideration of assessment time points recommended in the Food and Drug Administration Guidance[20] (approximately 30 days after the final dose) and the European Medicine Agency Guidelines[21] (at least 4 weeks after the final dose). In consideration of the potential effect of the residual drug in the blood on ADA assessment, blood will also be sampled at 1 time point, 225 days after the final dose of IMP, when plasma TEV-48125 concentrations are considered to be sufficiently decreased. Furthermore, blood will be collected at withdrawal. Consequently, blood will be collected from each subject at a maximum of 6 time points (a single time point for subjects enrolled for ADA assessment only).

3.7.4.3 Pharmacogenomics

3.7.4.3.1 DNA Storage

(1) Objectives

DNA will be stored to analyze CGRP and migraine-associated genes and to thereby examine their association with clinical treatment responses to TEV-48125 and their potential to be markers predictive of migraine severity and progression (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features).

(2) Target Patients

Only trial sites that have agreed in advance to collect samples for DNA storage will collect the samples from subjects who have provided written informed consent to the storage of their DNA samples among the subjects who receive IMP in this trial. DNA storage will not be performed for subjects enrolled for ADA assessment only. DNA

storage is voluntary. Even if a subject withdraws his/her consent to trial participation, the subject is not regarded as withdrawing his/her consent to DNA storage. DNA samples will be stored only if approval for DNA storage is obtained from the IRB/IEC/EC of a trial site. Consent to DNA storage will be obtained from subjects before blood is collected for DNA storage.

(3) Timing of Blood Sampling

- V2/Baseline (Day 1) or any of subsequent visits: Predose

(4) Blood Sampling and Storage Methods

Blood will be collected at the scheduled time points to obtain blood samples for DNA storage. The central laboratory will collect samples and assign a new personal code to each sample to make it double-coded. Then, DNA will be extracted from these samples. The central laboratory will transport DNA samples to the sample storage facility to store DNA. DNA samples will be stored until either when 1) genomic/genetic analysis is judged to be no longer necessary, 2) 15 years have passed since informed consent was obtained from the last subject, or 3) a subject withdraws consent for DNA storage, whichever is earlier. Upon request for destruction from the sponsor, the sample storage facility will destroy DNA samples in accordance with the relevant procedure specified by the facility.

Detailed procedures related to DNA samples are provided in Appendix 1. Blood sampling status (performed or not) and the date and time of blood sampling will be recorded on the CRF.

(5) Genomic/Genetic Analysis

Genomic/genetic analysis is performed only if it is considered useful to analyze CGRP and migraine-associated genes and to thereby examine their association with clinical treatment responses to TEV-48125 and their potential to be markers predictive of migraine severity and progression (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). If it is decided that genomic/genetic analysis is to be carried out, it will be performed in accordance with GCP after preparation of a separate protocol for pharmacogenomic research. The results of the analysis will not be included in the clinical study report but in the pharmacogenomic research report that is separately prepared.

Although target genes for genomic/genetic analysis may be genes having a potential association with CGRP and migraine, they are difficult to identify at this stage. Genomic/genetic analysis may include genome-wide association analysis performed using devices such as DNA chips, microarrays, and next-generation sequencers. Also in

this case, the results will not be used for any purposes other than those presented in Section 3.7.4.3.1 (1), Objectives. The genomic/genetic analysis facility will report the results of genomic/genetic analysis of double-coded samples to the sponsor.

Even if a subject withdraws from participation in the trial at his/her own request, the results of genomic/genetic analysis which have already been obtained before withdrawal will not be destroyed.

(6) Disclosure of the Results of Genomic/Genetic Analysis

As a result of genomic/genetic analysis, some genetic association may be found. However, the resulting findings would be exploratory in nature or at an early stage of research without sufficient scientific reliability in terms of accuracy, certainty, and other relevant elements. Given that the disclosure of scientifically ambiguous information would provide no benefits to subjects, the sponsor will not disclose the results of genomic/genetic analysis to subjects.

(7) Obtainment and Withdrawal of Consent to DNA Storage

Subjects will be asked to sign the ICF for DNA storage and genomic/genetic analysis using stored DNA samples. This consent form is prepared separately from the ICF for the trial. If a subject withdraws his/her consent to DNA storage during the DNA storage period, the sponsor will ask the sample storage facility to destroy the DNA sample from the subject. A subject's withdrawal from trial participation is not to be regarded as withdrawal of his/her consent to DNA storage. Upon request for destruction from the sponsor, the sample storage facility will destroy relevant DNA samples while maintaining their anonymity. Even if a subject withdraws from participation in the trial at his/her own request, the results of genomic/genetic analysis which have already been obtained before withdrawal will not be destroyed.

3.7.4.4 Biomarkers

(1) Objectives

Exploratory analysis may be conducted on inflammatory endpoints in blood to examine effects of TEV-48125 in patients with migraine. In addition, exploratory analysis of TEV-48125-related biomarkers may be conducted in terms of blood and urine biomarkers for extracellular matrix turnover, bone formation, bone resorption, and angiogenesis, in which involvement of CGRP is suspected. Biomarker samples will be stored for these exploratory analyses.

(2) Timing of Sampling

- V2/Baseline (Day 1): Predose
- V8/Month 6 (Day 169; acceptable window: ± 5 days): Predose
- V14/Month 12 (Day 337; acceptable window: ± 5 days): Predose

- Withdrawal (acceptable window: day of withdrawal decision + 7 days)
- V16/Follow-up (225 days after the final dose of IMP, acceptable window: ± 15 days)

(3) Sampling and Storage Methods

Blood and urine will be collected at the scheduled time points to obtain biomarker samples (plasma, serum, ribonucleic acid [RNA], urine). The central laboratory will collect samples and transport them to a sample storage facility. Biomarker samples will be stored until either when 1) exploratory biomarker analysis is judged to be no longer necessary or 2) 15 years have passed since informed consent was obtained from the last subject, whichever is earlier. Upon request for destruction from the sponsor, the sample storage facility will destroy relevant biomarker samples.

Detailed procedures related to biomarker samples are provided in Appendix 1.
Blood/urine sampling status (performed or not) and the date and time of blood/urine sampling will be recorded on the CRF.

(4) Exploratory Biomarker Analysis

Exploratory biomarker analysis is performed only if it is considered useful to analyze the relationship between effects of TEV-48125 in patients with migraine and inflammatory endpoints in blood and between TEV-48125 and blood and urine biomarkers for extracellular matrix turnover, bone formation, bone resorption, and angiogenesis, in which involvement of CGRP is suspected. If it is decided to carry out exploratory biomarker analysis, it will be performed in accordance with GCP after preparation of a separate protocol for exploratory biomarker analysis. The results of the analysis will not be included in the clinical study report but in the exploratory biomarker analysis report that is separately prepared.

While target biomarkers for exploratory biomarker analysis may be biomarkers for inflammation in blood, blood and urine biomarkers for extracellular matrix turnover, bone formation, or bone resorption, or blood biomarkers for endothelial generation or angiogenesis, they are difficult to identify at this stage. Extensive analysis may also be performed using a simultaneous multiple measurement panel. Also in this case, the results will not be used for any purposes other than those presented in Section 3.7.4.4 (1), Objectives.

Even if a subject withdraws from participation in the trial at his/her own request, the results of exploratory biomarker analysis which have already been obtained before withdrawal will not be destroyed.

3.7.5 End of Trial

The end of trial date for this trial is defined as the date of the last visit/contact or the date of the last attempt to contact, which is to be recorded on the follow-up page of the CRF prepared for the last subject who completes the trial (the end of trial date for individual subject is defined in Section 3.1, Type/Design of Trial).

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Discontinuation of Entire Trial

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to principal investigators, IRBs/IECs/ECs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Discontinuation at Individual Sites

Individual trial site participation may be discontinued by the sponsor, the principal investigator, or the IRB/IEC/EC if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The principal investigator will notify the sponsor promptly if the trial is terminated by the principal investigator or the IRB/IEC/EC at the trial site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 3.8.3.4, Procedures to Encourage Continued Trial Participation.

If any of the following discontinuation criteria is met and it is decided to discontinue treatment for a subject, examinations at the time of discontinuation specified in Section 3.7.1.2.11, Withdrawal (Acceptable Window: Day of Withdrawal Judgment + 7 Days), will be performed, and the date and reasons for discontinuation (see Section 3.8.3.2, Documenting Reasons for Treatment Discontinuation) will be recorded in the source documents and the CRF.

1) The subject's (or the subject's legal representative) requests for withdrawal.
2) Occurrence of an AE making continuation of IMP administration difficult.

3) The subject meets any of the discontinuation criteria specified in the Guidance on Safety Monitoring (see Appendix 4).
4) The subject uses or it is considered that the subject needs to use any prohibited concomitant medication or therapy.
5) The subject is found not to have met one or more of the inclusion criteria or to have fallen under any of the exclusion criteria.
6) The subject has failed to enter headache-related information at least 75% of the days in the electronic headache diary between the scheduled visits.
7) A marked deviation related to IMP administration is detected.
8) A female subject becomes pregnant, or is suspected of being pregnant, or desires to become pregnant (see Section 5.6, Pregnancy).
9) Other cases where it is considered by the investigator that the subject should discontinue treatment for reasons such as a difficulty in complying with the protocol

3.8.3.2 Documenting Reasons for Treatment Discontinuation

Concerning each subject undergoing treatment discontinuation, the investigator will choose one of the following main reasons for treatment discontinuation and record it on the CRF. If a subject discontinues trial treatment due to an AE, the investigator or other trial personnel will make every effort to follow the event until it has resolved or stabilized.

- Withdrawal by subject
- Withdrawal by parent/guardian
- Adverse event
  - Continuing IMP places the subject at undue risk as determined by the investigator because of the onset of an AE.
  - The subject meets any of the discontinuation criteria specified in the Guidance for Safety Monitoring (see Appendix 4).
- Protocol deviation
  - The subject uses or it is considered that the subject needs to use any prohibited concomitant medication or therapy.
  - The subject is found not to have met one or more inclusion criteria or to have fallen under any of the exclusion criteria.
  - The subject has failed to enter headache-related information at least 75% of the days in the electronic headache diary between the scheduled visits.
  - A marked deviation related to IMP administration is detected.
- Pregnancy
- Lost to follow-up
- Lack of efficacy
- Site terminated by sponsor

- Study terminated by sponsor
- Other

3.8.3.3 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without any disadvantage. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow up (these methods of follow up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol-specified follow-up procedures (a part of follow-up procedures for which the subject withdraws his/her permission, as agreed by subject and trial personnel).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source documents as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express his/her desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.1, Treatment Discontinuation). A subject may, however, indicate that further trial participation is creating a burden on his/her work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.2,

Documenting Reasons for Treatment Discontinuation to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

3.8.3.4 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

3.9 Screen Failures

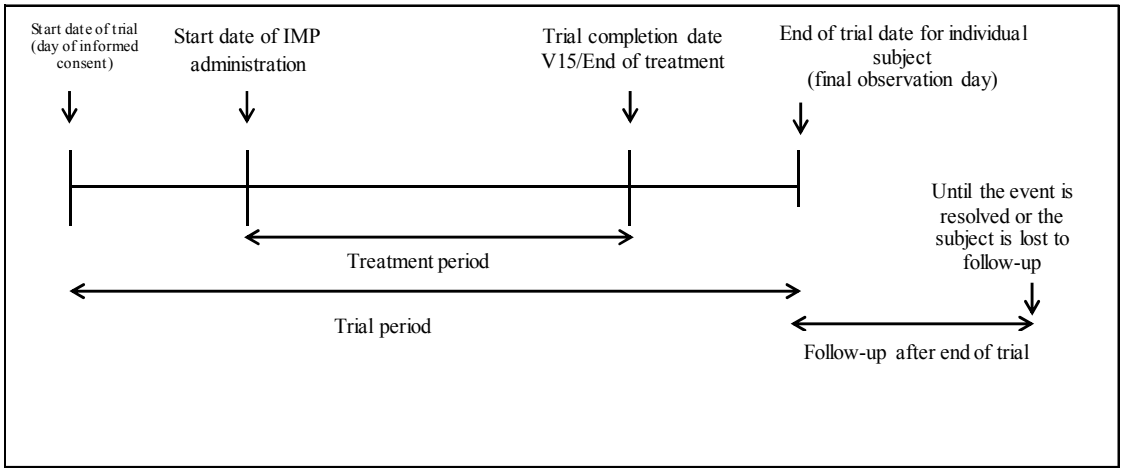
A screen failure subject is one from whom written informed consent is obtained but who is not randomized in the trial.

If the subject meets the definition of a screen failure, the following information will be recorded on the CRF:

- Visit date
- Date of informed consent
- Date of investigation
- Birth date
- Sex
- Race
- Ethnicity
- Country
- Results of assessment for eligibility criteria (if the subject is found to be ineligible, the number of the criterion that renders the subject ineligible will be recorded.)
- Date of assessment as a screen failure
- Reason for screen failure

3.10 Definition of Completed Subjects

Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For the purposes of this trial, subjects who complete assessments at V15/End of treatment will be defined as trial completers.



3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before V15/End of treatment during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Subjects who do not return to the trial site for V16/Follow-up will also be defined as subjects lost to follow-up. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The trial site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Protocol Deviations

In the event of a deviation from the protocol due to an emergency, accident, or mistake (eg, noncompliance with GCP guidelines, violation of IMP assignment or treatment compliance, violation of inclusion/exclusion criteria or discontinuation criteria, or violation of concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. The investigator will record any protocol deviation on the source documents. Any major

protocol deviation will be recorded on the CRF along with the date and details of the deviation.

4 Restrictions

Use of the following medications and concomitant therapies will be prohibited or restricted from after informed consent (or after V1/Screening if the date of informed consent and V1/Screening fall on a different day) to V15/End of treatment or the time of withdrawal. Restrictions in regard to pregnancy and sexual activity are detailed in Section 3.4.3, Exclusion Criteria. Male patients may not donate sperm during the trial and for 225 days after the final dose of IMP.

The prohibitions and restrictions related to medications and concomitant therapies specified in the following sections will not apply to subjects enrolled for ADA assessment only. However, these subjects will be subject to restrictions in regard to pregnancy and sexual activity, similarly to those who receive the IMP, for 225 days after the final dose of IMP in the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002).

4.1 Prohibited/Restricted Medications

Subjects will be allowed to use acute headache medication only at the time of occurrence of a headache attack, as needed, but will not be allowed to use it as preventive medication.

Use of other medications that belong to the same classes as those of prohibited or restricted medications but are not included in Table 4.1.1-1 or Table 4.1.2-1 are allowed.

4.1.1 Prohibited Medications (Preventive Migraine Medications)

Use of any preventive migraine medications other than the IMP (see Table 4.1.1-1) will be prohibited.

Table 4.1.1-1 List of Prohibited Concomitant Medications (Preventive Migraine Medications)

Drug Class	Drug Name	Remarks
Antiepileptic medications	Carbamazepine	
Angiotensin receptor blockers/ angiotensin converting enzyme inhibitors	Candesartan and lisinopril	
Onabotulinumtoxin A	Botox	
Triptans/ergot derivatives	Ay drug in this class	Should not be used as preventive therapy for migraine
NSAID	Ay drug in this class	Should not be used as preventive therapy for migraine or on a daily basis for other indications

NSAID = nonsteroidal anti-inflammatory drug.

Any of the medications listed above are allowed if given as a topical preparation or eye drops.

4.1.2 Restricted Concomitant Medications (Preventive Migraine Medications)

A small subgroup of subjects will be allowed to use no more than 2 concomitant preventive migraine medications (see Table 4.1.2-1) at a stable dose and regimen during the trial if the medications were previously prescribed for migraine or for another indication. However, such subjects on preventive medication must be on a stable dose and regimen for at least 2 months of consecutive use prior to informed consent. Subjects will be allowed to discontinue the use of preventive medication if discontinuation is considered clinically necessary by the investigator (for reasons such as they are no longer needed or they are associated with safety concerns). In such a case, reasons for discontinuation should be recorded.

In principle, use of medicines (including Chinese herbal medicines) or supplements that are regarded as effective for preventing migraine will be allowed if they were previously used before informed consent. Subjects on such medicines or supplements should be on a stable dose and regimen in so far as possible.

Table 4.1.2-1 List of Restricted Concomitant Medications (Preventive Migraine Medications)

Drug Class	Drug Name
Beta-blockers	Atenolol, propranolol, metoprolol, nadolol, and timolol
Calcium channel blocker/benzocycloheptene	Lomerizine
Antidepressants	Amitriptyline, venlafaxine, nortriptyline, and duloxetine
Antiepileptic medications	Topiramate and valproate

Any of the medications listed above are allowed irrespective of restriction conditions if given as a topical preparation or eye drops.

4.2 Prohibited Concomitant Therapies

Use of an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for treating migraine will be prohibited.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

An SAE includes any event that results in any of the following outcomes.

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other non-medical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. Any potential drug-induced liver injury (DILI) case (AST or ALT $\geq 3 \times$ upper limit of normal [ULN], and total bilirubin $\geq 2 \times$ ULN or INR > 1.5) is considered an SAE even if it does not require hospitalization.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

An immediately reportable event (IRE) is any of the following:

- Any SAE.

- Any AE experienced by investigators or other trial personnel during handling of the IMP
  (example: A nurse has accidental eye contact with an injection solution, which causes dacryorrhea.)
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication.
- Any ophthalmic AE of at least moderate severity
- Any event of suspected anaphylaxis or severe hypersensitivity reaction
- Any infection caused by a biological pharmaceutical/IMP that is contaminated or suspected of being contaminated with viruses such as HBV, HCV, and HIV. Seasonal infections such as the common cold are not included.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the CRF. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the non-leading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRFs provided by the sponsor. Adverse events and SAEs are to be collected during the period from the time a subject signs the ICF to the end of trial date for individual subject. Also for subjects enrolled for ADA assessment only, AEs will be collected during the period from the time a subject signs the ICF for this trial to the end of trial date for individual subject in a similar manner. Furthermore, any AE that has not resolved by the end date of either of the phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) will be followed in this trial, and its latest outcome as of the end date of this trial is to be recorded on source documents and the CRF provided by the sponsor.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Any reported AE for which the severity or seriousness has changed after reporting should be reported as a new AE on the CRF.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined in Section 5.3, Immediately Reportable Events (IREs). Special attention should be paid to recording hospitalization or concomitant medications.

5.3 Immediately Reportable Events (IREs)

The investigator must report within 24 hours after either the investigator or designee becomes aware of any IRE (see Section 5.1, Definitions) by telephone, fax, or e-mail to the sponsor (for contact information, see the cover page of this protocol). An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is not the AE page of the CRF.) When sending an IRE form by e-mail, etc, sufficient care and attention must be taken to protect subject privacy.

Subjects experiencing SAEs should be followed clinically until the events are resolved, stabilized, or the subject is lost to follow-up. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. It is expected

that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Drug-induced Liver Injury

See Appendix 4 for guidance on how to monitor subjects with increased liver function test values. Any potential DILI case (AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN or INR > 1.5) requires immediate withdrawal from the trial. All values measured in accordance with the guidance on monitoring will be recorded on an IRE form, and the case will be recorded on the CRF as an AE.

5.5 Events of Suspected Anaphylaxis or Severe Hypersensitivity Reaction

Severe hypersensitivity reactions will be monitored using the diagnostic clinical criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis[22] (see Appendix 2). In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.

5.6 Pregnancy

Women of child-bearing potential (WOCBP) are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months since last menses and whose FSH level is higher than 35 U/L).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures (ie, double-barrier method) to prevent pregnancy during the course of the trial and for 225 days after the final dose of IMP. Unless the subject or their partner is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months since last menses and whose FSH level is higher than 35 U/L; or men who have had a bilateral orchidectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pills, birth control depot injection, birth control implant, condom with spermicide, or sponge with spermicide. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- ICF
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

A serum HCG test will be performed at V1/Screening on all WOCBP.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum HCG tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the serum HCG is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 225 days after the final dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Clinical Trial Pregnancy and Breastfeeding Exposure Form for monitoring the outcome of the pregnancy (including spontaneous or elective abortion).

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Clinical Trial Pregnancy and Breastfeeding Exposure Form, follow-up information regarding the course of the

pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the birth date.

5.7 Procedure for Breaking the Blind

Not applicable.

5.8 Follow-up of Adverse Events

For this trial, information on AEs will be collected for the period from the time the subject signs the informed consent form until the end of trial date for individual subject (the last scheduled contact). Even after the end of trial date for individual subject, AEs that meet any of the cases described in Section 5.8.1, Follow-up of Nonserious Adverse Events, through Section 5.8.3, Follow-up and Reporting of Serious Adverse Events Occurring After End of Trial Date for Individual Subject (Last Scheduled Contact, will be followed as specified in the relevant section.

5.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE CRF with the current status noted. If a subject has an AE whose causal relationship with the IMP cannot be ruled out or has not recovered from an AE at the end of trial date for individual subject (the last scheduled contact), follow-up contacts will be performed until the event is resolved, stabilized, or the subject is lost to follow-up. All nonserious events that are ongoing at the end of trial date for individual subject (the last scheduled contact) will be recorded as ongoing on the CRF and follow-up information obtained after the end of trial date for individual subject (the last scheduled contact) will be recorded in the subject's medical record. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.8.2 Follow-up of Serious Adverse Events

This trial requires that subjects be actively monitored for SAEs for the period from the time of the subject's signing the ICF until the end of trial date for individual subject (the last scheduled contact).

Serious AEs that are identified or ongoing at the end of trial date for individual subject (the last scheduled contact) must be recorded on the AE CRF page and reported to the sponsor according to the reporting procedures outlined in Section 5.3, Immediately Reportable Events (IREs). This may include unresolved previously reported SAEs, or new SAEs. Any SAE that is ongoing at the end of trial date for individual subject (the

last scheduled contact) is recorded as ongoing on the CRF. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event is resolved, stabilized, or the subject is lost to follow-up using an IRE form.

5.8.3 Follow-up and Reporting of Serious Adverse Events Occurring After End of Trial Date for Individual Subject (Last Scheduled Contact)

Any new SAEs reported by the subject to the investigator that occur after the end of trial date for individual subject (the last scheduled contact), and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs that are captured on follow-up telephone contact or at any other time point after the defined trial period (ie, up to end date of the period of trial participation [the end of trial date for individual subject]). The investigator should follow SAEs identified after the end of trial date for individual subject (the last scheduled contact) until the events are resolved, stabilized, or the subject is lost to follow-up. The investigator should continue to report any significant follow-up information to the sponsor up to the point the event has been resolved or stabilized, or the subject is lost to follow-up using an IRE form.

6 Pharmacokinetic/pharmacodynamic/pharmacogenomic Analysis

6.1 Pharmacokinetics

6.1.1 Pharmacokinetic Analysis Set

(1) 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 IMP in Trial 406-102-00002 and in whom an effective plasma drug concentration is measured for at least one postdose time point in the present trial will be included.

(2) 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 IMP in either the present trial, Trial 406-102-00001, or

Trial 406-102-00002 and in whom an effective plasma drug concentration is measured for at least one postdose time point in the present trial will be included.

6.1.2 Pharmacokinetic Analysis

(1) Endpoint
Plasma TEV-48125 concentration

(2) Dataset for Analysis
Pharmacokinetic analysis sets (PKS 1 and PKS 2)

(3) Analysis Method

1) Acceptance or nonacceptance of data will be determined in accordance with Section 3.4, Exclusion from Pharmacokinetic Analysis, of the Manual Standard Practice for Noncompartmental Pharmacokinetic Analysis (Version 1.0).[23]
2) Concerning Section 6.1.2 (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 for plasma drug concentrations include the number of subjects, arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

6.2 Immunogenicity

6.2.1 Immunogenicity Analysis Set

(1) 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 IMP in Trial 406-102-00002 and in whom serum ADA is measured for at least one postdose time point in the present trial will be included.

(2) 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 IMP in either the present trial, Trial 406-102-00001, or Trial 406-102-00002 and in whom serum ADA is measured for at least one postdose time point in the present trial will be included.

6.2.2 Immunogenicity Analysis

Summary of immunogenicity results will be provided, and the incidence of immunogenicity expression will be calculated separately for IGS 1 and IGS 2.

6.3 Pharmacogenomics

For analyses related to pharmacogenomics, see Section 3.7.4.3.1 (5), Genomic/genetic Analysis.

6.4 Biomarkers

For analyses related to biomarkers, see Section 3.7.4.4 (4), Exploratory Biomarker Analysis.

7 Statistical Analysis

7.1 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, Trial Rationale). 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).

7.2 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 for whom electronic headache diary efficacy assessment data at baseline and after the first dose of IMP are available

7.3 Handling of Missing Data

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

7.4 Analysis of Demographic and Baseline Characteristics

For demographic and baseline characteristics, either descriptive statistics will be calculated or frequency distribution will be obtained overall and by treatment group, according to the nature of characteristics, using the RS as the analysis set.

7.5 Safety Analysis

Safety analysis will be performed using the SS as the analysis set unless otherwise stated.

7.5.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized overall and by treatment group:

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The above summaries will also be prepared for TEAEs potentially causally related to the IMP.

7.5.2 Clinical Laboratory Data

For clinical laboratory data and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated overall and by treatment group.

For the numbers of subjects with clinical laboratory data meeting the criteria for potentially clinically significant values, frequency distributions will be obtained overall and by treatment group.

7.5.3 Vital Signs and Weight Data

For vital sign and weight measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated overall and by treatment group. In addition, for the numbers of subjects with data meeting the criteria for potentially clinically significant values in each treatment group, frequency distributions will be obtained.

7.5.4 Twelve-lead Electrocardiogram Data

For ECG measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated overall and by treatment group. For the results of assessments, a shift table from baseline will be displayed.

7.5.5 Injection Site Reactions

For severities of the injection site reactions (erythema, induration, ecchymosis, and pain), frequency distributions will be obtained overall and by treatment group.

7.5.6 Electronic Columbia-Suicide Severity Rating Scale

A list will be prepared for subjects with suicidal ideation and behavior.

7.6 Efficacy Analysis

The efficacy endpoints in this trial are as follows:

- Number of migraine days
- Number of headache days of at least moderate severity
- Number of headache days of any severity
- Number of days with use of acute headache medications
- Number of subjects discontinuing concomitant preventive migraine medications during the treatment period
- Number of days with nausea or vomiting
- Number of days with photophobia or phonophobia
- HIT-6 (for subjects with CM only)
- MIDAS (for subjects with EM only)
- MSQOL
- EQ 5D-5L
- PGIC

- PHQ-2 and PHQ-9
- WPAI

Efficacy data will be summarized by treatment group, using the FAS as the analysis set.

7.6.1 Interim Analysis

An interim analysis may be performed 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 conducting the final analysis of this trial.

8 Management of Investigational Medicinal Product

For full details on IMP management, see the TEV-48125 Investigator's Brochure.

Each 2.25 mL prefilled syringe (with a staked 27 G ½" needle) for single-use administration contains TEV-48125 225 mg/1.5 mL (150 mg/mL).

8.1 Packaging and Labeling

Trial medication will be supplied to the principal investigators or the persons designated by the principal investigators or trial sites by the sponsor or a designated agent. The IMP will be supplied as packages containing a prefilled syringe. Each package to be used in the dosing period will be labeled to clearly disclose compound code, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements, etc.

8.2 Storage

The IMP will be stored in a place where security is assured (eg, locked refrigerator). Access will be limited to principal investigators and their designees. Neither principal investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored at 2°C to 8°C, protected from light.

The trial site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The principal investigator or designee must maintain an inventory record of IMP received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused IMP must be returned to the sponsor or a designated agent.

All IMP returned to the sponsor must be accompanied by appropriate documentation and be identified by protocol number with trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of unused IMP.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Syringe defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail (email address: PQC_406-102-00003@otsuka.jp) immediately after becoming aware of the PQC according to the procedure outlined in Section 8.5.2 (Information Required for Reporting Purposes).

Identification of a PQC by the subject should be reported to the investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of compliant

- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, Kit number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Complaint sample availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If a complaint sample is available for return, the sponsor will provide instructions for sample return, when applicable.

It must be documented in the trial site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, recorded data from automated instruments, electronic headache diary, and ePRO. All source documents pertaining to this trial will be maintained by the principal investigators and made available for direct inspection by authorized persons. Principal investigators/trial sites will permit trial-related monitoring, audits, IRB/IEC/EC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the trial site, the investigator will record all significant observations and findings in the subject's medical records. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;

- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each investigator (or designee) who made an entry in the medical records.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the medical records as described above. Any changes to information in the medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documents by the investigator. If electronic data systems are being utilized, a full audit trail of changes must be maintained.

Information from the medical records and other source documents will be entered by trial site staff directly onto electronic CRFs in the sponsor's electronic data capture (EDC) system. Changes to the data will be captured by an automatic audit trail. If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, electronic headache diary, and ePRO), the results will be sent to the trial site where they will be retained, but not entered into the EDC unless otherwise noted in the protocol. These data will also be sent electronically to the sponsor from each source. Changes to the data will be captured by an automatic audit trail in the source system.

9.3 File Management at the Trial Site

The principal investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The principal investigator/trial site will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating principal investigators maintain detailed clinical data for the longest of the following 4 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the principal investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.
  If regional requirements are longer, the specific information for the region should be stated in the trial's Operations Manual or the principal investigator's contract.
- Determination of the period until the termination of DNA storage or biomarker sample storage.

The principal investigator must not dispose of any records relevant to this trial without either 1) written permission from the sponsor or 2) provision of an opportunity for sponsor to collect such records. The principal investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the principal investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the trial site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site staff will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The principal investigator agrees to cooperate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The principal investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB/IEC/EC according to regional requirements, and the principal investigator will provide that documentation to the sponsor. The IRB/IEC/EC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs, IRE forms, etc, the investigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the principal investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in CRFs. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The principal investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC/EC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC/EC, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB/IEC/EC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and principal investigator, followed by IRB/IEC/EC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC/EC, principal investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC/EC, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Principal investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, principal investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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Appendix 1 Handling and Shipment of Bioanalytical Samples

(1) Handling of Samples

A label will be firmly attached to each sample storage tube. The label contains the following information: protocol number, subject identification number, visit number (eg, V2/Baseline, V3/Month 3), sampling date, sampling timing (eg, before administration), sample type (eg, pharmacokinetics, ADA, DNA, or serum for biomarkers), and aliquot number (eg, Aliquot 1, Aliquot 2). Instead of the planned sampling time point, the time at which specimens were actually sampled should be accurately entered on the case report form.

(2) Handling and Shipment of Pharmacokinetic Samples

Six milliliters of blood will be collected via venipuncture or indwelling catheter into a dipotassium ethylenediaminetetraacetic acid (EDTA) collection tube. Then, the collection tube will be inverted slowly 8 to 10 times to mix the content and will be placed in ice water. This sample will be centrifuged (approximately 1300 × G) at approximately 4ºC for approximately 10 minutes between 5 minutes and 1 hour after blood collection. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Plasma will be aliquoted by a standard experimental procedure into 2 appropriately labeled tubes for storage (Aliquot 1 and 2). The 2 aliquots of the same plasma sample will be stored in a freezer at a temperature of below −20ºC or −70ºC within 60 minutes of the end of centrifugation. Within 3 days after sampling, the central laboratory will collect plasma sample Aliquots 1 and 2 and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice. The central laboratory will transport Aliquot 1 plasma samples to the drug concentration measurement facility in accordance with instructions of the sponsor. The central laboratory will store Aliquot 2 plasma samples until the clinical study report is issued unless otherwise instructed by the sponsor.

(3) Handling and Shipment of ADA Samples

Blood will be collected via venipuncture or indwelling catheter into a collection tube containing no anticoagulant (containing a coagulation accelerator, 5 mL). Blood collected will be left to stand at room temperature for approximately 30 minutes to allow for coagulation and serum separation to occur. The sample will then be centrifuged (approximately 1300 × G) at approximately 4ºC for approximately 10 minutes within 1.5 hours of sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Serum will be aliquoted by a standard experimental procedure into 2 appropriately labeled tubes for storage (Aliquot 1 and 2). The 2 aliquots of the same serum sample will be stored in a freezer at a temperature of below −20ºC or

−70ºC within 60 minutes of the end of centrifugation. Within 3 days after sampling, the central laboratory will collect serum sample Aliquots 1 and 2 and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice. The central laboratory will transport Aliquot 1 serum samples to the ADA measurement facility in accordance with instructions of the sponsor. The central laboratory will store Aliquot 2 serum samples until the clinical study report is issued unless otherwise instructed by the sponsor.

(4) Handling and Shipment of DNA Samples

Six milliliters of blood will be collected via venipuncture or indwelling catheter into a dipotassium EDTA collection tube. Then, the collection tube will be inverted slowly 8 to 10 times to mix the contents. The blood sample will be transferred into an appropriately labeled tube for storage. The blood sample will be stored in a freezer at a temperature of below −20ºC or −70ºC within 60 minutes of sampling. Within 3 days after sampling, the central laboratory will collect blood samples and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice. The central laboratory will assign a new personal code to each sample to make it double-coded. Then, DNA will be extracted from these samples. DNA samples will be stored in a freezer at a temperature of below −70ºC.

(5) Handling and Shipment of Serum Samples for Biomarkers

Blood will be collected via venipuncture or indwelling catheter into a collection tube containing no anticoagulant (containing a coagulation accelerator, 6 mL). Blood collected will be left to stand at room temperature for approximately 30 minutes to allow for coagulation and serum separation to occur. The sample will then be centrifuged (approximately 1300 × G) at approximately 4ºC for approximately 10 minutes within 1.5 hours of sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Serum will be transferred by a standard experimental procedure into an appropriately labeled tube for storage. The serum sample will be stored in a freezer at a temperature of below −20ºC or −70ºC within 60 minutes of the end of centrifugation. Within 3 days after sampling, the central laboratory will collect serum samples and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice.

(6) Handling and Shipment of Plasma Samples for Biomarkers

Six milliliters of blood will be collected via venipuncture or indwelling catheter into a dipotassium EDTA collection tube. Then, the collection tube will be inverted slowly 8 to 10 times to mix the content and will be placed in ice water. The sample will then be

centrifuged (approximately 1300 × G) at approximately 4ºC for approximately 10 minutes between 5 minutes and 1 hour after blood collection. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Plasma will be transferred by a standard experimental procedure into an appropriately labeled tube for storage. The plasma sample will be stored in a freezer at a temperature of below −20ºC or −70ºC within 60 minutes of the end of centrifugation. Within 3 days after sampling, the central laboratory will collect plasma samples and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice.

(7) Handling and Shipment of RNA Samples for Biomarkers

Blood (7.5 mL) will be collected via venipuncture or indwelling catheter into a PAXgene® Blood RNA Tube (2.5 mL) for collection. Then, the collection tube will be inverted slowly 8 to 10 times to mix the content and will be left to stand in an upright position at room temperature for approximately 2 hours. The blood sample will then be transferred into an appropriately labeled tube for storage, and stored at a temperature of below −20ºC or −70ºC. Within 3 days after sampling, the central laboratory will collect the blood sample and store it in a freezer at a temperature of below −70ºC. During transfer, the sample will be placed in a well-insulated container filled with a sufficient amount of dry ice.

(8) Handling and Shipment of Urine Samples for Biomarkers

Urine will be collected in a urine sampling cup after the first brief miction (a few milliliters) is discarded. Approximately 10 mL of urine will be collected in a polypropylene container. Within 60 minutes of sampling, the urine sample will be stored in a freezer at a temperature of below −20ºC or −70ºC. Within 3 days after sampling, the central laboratory will collect urine samples and store them in a freezer at a temperature of below −70ºC. During transfer, all samples will be placed in a well-insulated container filled with a sufficient amount of dry ice.

Appendix 2 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3) Reduced BP after exposure to known allergen for that subject (minutes to several hours):
   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Source: Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. [reprint in Ann Emerg Med. 2006;47(4):373-80]. J Allergy Clin Immunol. 2006;117(2):391-7.

Appendix 3 ICHD-3 beta Diagnostic Criteria

For further details, refer to Classification Committee of the IHS, 2013[1].

1.1 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B through D
B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following 4 characteristics:
   - unilateral location
   - pulsating quality
   - moderate or severe pain intensity
   - aggravation by, or causing avoidance of, routine physical activity (eg, walking or climbing stairs)
D. During headache, at least 1 of the following:
   - nausea and/or vomiting
   - photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

1.2 Migraine With Aura

A. At least 2 attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   - visual
   - sensory
   - speech and/or language
   - motor
   - brainstem
   - retinal
C. At least 2 of the following 4 characteristics:
   - at least 1 aura symptom spreads gradually over ≥ 5 minutes, and/or 2 or more symptoms occur in succession
   - each individual aura symptom lasts 5 to 60 minutes
   - at least 1 aura symptom is unilateral
   - the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

[1] Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629-808.

Appendix 4 Guidance on Safety Monitoring

Guidance on Monitoring Patients With Elevated Liver Function Tests

Liver enzymes (ALT, AST, GGT, and ALP) as well as total bilirubin and direct bilirubin will be measured (and indirect bilirubin will be calculated) at each trial visit.

In any case of elevated ALT or AST to a level exceeding ≥ 2× the ULN (including patients whose baseline ALT or AST levels are ≥ 2 × and ≤ 3 × the ULN, who may be enrolled in the trial), a thorough medical history should be taken and a physical examination with a focus on liver disease should be performed.[1] In addition, the patient should be instructed to refrain from alcoholic beverages.

In cases where the symptoms are compatible with drug-induced liver injury during the trial, patients will be instructed to return to the trial site for an unscheduled visit to measure liver enzymes as soon as possible. Solitary elevations of total or direct bilirubin, not accompanied by elevations of ALT or AST, should be managed based on the judgement of the treating physician.

In line with Section 3.7.3.2, Clinical Laboratory Assessments, all blood testing will be performed at the central laboratory. The day on which the abnormal value is received from the central laboratory will be considered as Day 0.

Elevation of Either ALT or AST to ≥ 3× ULN

Confirmation is required prior to investigational medicinal product (IMP) discontinuation in cases of elevation of either ALT or AST ≥ 3× ULN (Note: In cases of elevation of ALT or AST ≥ 8× the ULN, no confirmation is required prior to IMP discontinuation, but the assessments below should be performed). The following procedures should be followed:

- The investigator should repeat the test for confirmation purposes [ALT, AST, ALP, total and direct bilirubin, complete blood count (CBC) (with differential for

[1] Thorough medical history with a focus on liver disease: personal or family history of liver disease; personal history of a systemic disease with potential liver involvement; exposure to alcohol, medications (prescription or over-the-counter), herbal preparations, dietary supplements, recreational drugs, special diets, or environmental chemical agents; potential exposure to infectious agents (eg, travel to developing countries, history of potential exposure to blood or blood products, high-risk sexual relations); and any additional information deemed relevant by the principal investigator. Physical examination, including signs of chronic liver disease.

eosinophil count), and INR]. The investigator should also question the patient regarding symptoms.

The abnormality will be regarded as confirmed in each of the following scenarios:

- The baseline value was within the normal range and ALT or AST is still ≥ 3 × the ULN.
- The baseline value was above the ULN and ALT or AST is ≥ 2 × the baseline value.

Additional Tests/Evaluations:

Upon confirmation of the abnormality as noted above, the following additional evaluations should be performed

- Serology for hepatitis A (antibody and immunoglobulin M [IgM] and IgG), B (core antibody total, core IgM, and surface antigen), and C (antibody) viruses
- Serology for autoimmune hepatitis: antinuclear antibodies (titer), antismooth muscle antibodies, and antiliver kidney microsomal antibodies
- Ultrasound examination of the liver and biliary tract at the investigator's discretion (date of examination and the normality/abnormality judgment will be recorded in CRF)
- Observation and follow-up (to be performed after the abnormality was confirmed as above)

ALT or AST ≥ 3 × (> 3.5 × the ULN if the Baseline Value Is > 2.5 × the ULN) but Less Than 5 × the ULN

In addition to the above procedures required for any elevation to levels > 3 × the ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC (including differential), and INR should be monitored on Days 5 (± 2 days), 8 (± 2 days), 14 (± 3 days), and 28 (± 3 days).
- Should the abnormality (≥ 3 × the ULN in cases where the baseline value was within the normal range or ≥ 2 × the ULN in cases where the baseline value was above ULN but still < 5 × the ULN) persist, the patient will be followed at the investigator's discretion, but ALT, AST, GGT, ALP, and total and direct bilirubin should be monitored.

ALT or AST ≥ 5 × but Less Than 8 × the ULN

In addition to the above procedures required for any elevation to levels > 3 × the ULN:

- ALT, AST, GGT, ALP, total and direct bilirubin, CBC (including differential), and INR should be monitored twice a week.

ALT or AST ≥ 8 × the ULN

In addition to the above procedures required for any elevation to levels > 3 × the ULN:

- The IMP should be discontinued immediately, and the early withdrawal visit should be performed.
- For follow-up guidance, please see section below "Follow-up of Liver Enzymes After Stopping Rules Are Met."

Stopping Rules

In the following circumstances, the IMP will be discontinued immediately:

- Any increase in ALT or AST to ≥ 3 × the ULN, combined with INR > 1.5 × the ULN or total bilirubin > 2 × the ULN
- Any increase in ALT or AST to ≥ 3 × the ULN, which is accompanied by symptoms clearly associated with impaired liver function (eg, vomiting, nausea, fever, rash, eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by migraine)
- Any increase in ALT or AST to levels ≥ 5 but < 8 × the ULN, which is persistent for ≥ 2 weeks of repeated measurements
- Any increase in ALT or AST to levels ≥ 8 × the ULN
- In any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

Follow-up of Liver Enzymes After Stopping Rules Are Met

- A patient who meets the above criteria for discontinuation of the IMP should be invited to the trial site to return the IMP. Withdrawal visit activities should be performed as soon as possible.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, based on the judgment of the investigator.
- In any case, following the withdrawal visit, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least once weekly.

Every effort should be made to complete the additional tests/evaluations, as described above.

Appendix 5 Protocol Amendments/Administrative Changes

Amendment Number: 1

Issue Date: 30 Nov 2017

PURPOSE:

To clarify the text and revise written errors and the like

BACKGROUND:

Revisions were made because unclear text, written errors and the like were found.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
3.1 Type/Design of Trial	After obtaining written informed consent from patients (Visit [V] 1/Screening), the investigator will screen them for eligibility.	After obtaining written informed consent from patients, the investigator will screen them for eligibility (Visit [V] 1/Screening).
3.2 Trial Treatments	IMP should be removed from the refrigerator and allowed to equilibrate at room temperature for 15 to 30 minutes before IMP administration.	IMP should be removed from the refrigerator and allowed to equilibrate at room temperature for 45 to 60 minutes before IMP administration.
Protocol Synopsis Inclusion/Exclusion Criteria: 3.4.2 Table 3.4.2-1 Inclusion Criteria, No. 6	Not using preventive medications (see Table 4.1.1-1) (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medications (see Table 4.1.2-1) for migraine or other medical condition (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent.	Not using preventive migraine medications (prohibited or restricted medications, see Table 4.1.1-1 and Table 4.1.2-1) for migraine or other medical conditions (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medication (restricted medications, see Table 4.1.2-1) for migraine or other medical conditions (eg, propranolol used for hypertension) if the dose and regimen have been stable for at least 2 months prior to giving informed consent.
3.7.1; Table 3.7.1-1 Schedule of Assessments for Subjects Receiving	(No footnote marker)	A footnote marker, “a”, has been added to “X” in the “Informed consent” column for “Screening Period”. Accordingly, all other footnote markers have been updated.

Protocol Section	Before Revision	After Revision
IMP		
3.7.1; Table 3.7.1-1 Schedule of Assessments for Subjects Receiving IMP (footnote)	(No footnote)	The following footnote has been added: [a]Informed consent can be obtained prior to the day of V1/Screening. Accordingly, all other footnote markers have been updated.
3.7.1.1 Screening Period	The screening period begins at V1/Screening and ends on the day before V2/Baseline.	The screening period begins on the day of informed consent and ends on the day before V2/Baseline. An appropriately signed and dated ICF will be obtained before screening procedures commence. After informed consent is obtained, the investigator (or designee) will promptly enter the subject's information in the IRT and obtain a subject identification number as described in Section 3.3.2, Subject Selection and Numbering. The following information will be recorded on the case report form (CRF): • Informed consent – Date of informed consent – Subject identification number
3.7.1.1.1 Visit 1/Screening (Day −28; Acceptable Window: −5 Days)	An appropriately signed and dated ICF will be obtained before screening procedures commence. After informed consent is obtained, the investigator (or designee) will promptly enter the subject's information in the IRT and obtain a subject identification number as described in Section 3.3.2, Subject Selection and Numbering. V1/Screening will take place 28 days before V2/Baseline. In order to determine the subject's eligibility, the following assessments/tests/observations will be performed and recorded on the case report form (CRF). • Visit date • Informed consent – Date of informed consent – Subject identification number • Result of eligibility assessment • Demographics – Date of investigation	V1/Screening will take place 28 days before V2/Baseline. In order to determine the subject's eligibility, the following assessments/tests/observations will be performed and recorded on the CRF. • Visit date • Result of eligibility assessment • Demographics – Date of investigation – Birth date, age, and sex (at the time of informed consent) – Childbearing potential (Reason for nonchildbearing potential, or contraceptive methods) – Race, ethnicity, and country – Medical history and complications (at the time of informed consent)

Protocol Section	Before Revision	After Revision
	– Birth date, age, and sex – Childbearing potential (Reason for nonchildbearing potential, or contraceptive methods) – Race, ethnicity, and country – Medical history and complications	
4 Restrictions	Use of the following medications and concomitant therapies will be prohibited or restricted from after informed consent to V15/End of treatment or the time of withdrawal.	Use of the following medications and concomitant therapies will be prohibited or restricted from after informed consent (or after V1/Screening if the date of informed consent and V1/Screening fall on a different day) to V15/End of treatment or the time of withdrawal.
4.1.2 Restricted Concomitant Medications (Preventive Migraine Medications)	A small subgroup of subjects will be allowed to use no more than 2 concomitant preventive migraine medications (see Table 4.1.2-1) during the trial if the medications were previously prescribed for migraine or for another indication.	A small subgroup of subjects will be allowed to use no more than 2 concomitant preventive migraine medications (see Table 4.1.2-1) at a stable dose and regimen during the trial if the medications were previously prescribed for migraine or for another indication.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Amendment Number: 2

Issue Date: 19 Jun 2018

PURPOSE:

To reflect the changes made after the discovery of an error in the IRT system in the phase 2b/3 trial in EM patients (Trial 406-102-00002) and to clarify the text, correct errors, resolve inconsistencies throughout the text, reflect changes in the statistical analysis plan, etc.

BACKGROUND:

As a result of an error in the IRT system in the phase 2b/3 trial in EM patients (Trial 406-102-00002), the subject population and other sections of this protocol were revised. Revisions were also made because unclear text errors, etc, were found. Furthermore, on the basis of results from the global studies, it was considered that stratified analysis would not be applicable.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
Protocol Synopsis, Subject Population	(2) Up to 870 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, respectively)	(2) Up to 966 subjects who have completed or discontinued phase 2b/3 trials in patients with CM or EM (Trials 406-102-00001 and 406-102-00002, respectively)
Protocol Synopsis, Criteria for Evaluation; 3.5.2 Efficacy Endpoints; 7.6 Efficacy Analysis	• Number of days of use of any acute migraine medications	• Number of days with use of any acute headache medications
Protocol Synopsis, Criteria for Evaluation; 3.5.2 Efficacy Endpoints; 7.6 Efficacy Analysis	(Not included)	• Number of days with nausea or vomiting • Number of days with photophobia or phonophobia
Protocol Synopsis, Statistical Methods	[Safety analysis] Safety endpoint data will be summarized by disease subtype (CM or EM) and by	[Safety analysis] Safety endpoint data will be summarized overall and by treatment group in the

Protocol Section	Before Revision	After Revision
	treatment group in the safety analysis set.	safety analysis set.
Protocol Synopsis, Trial Duration	Planned trial participation period for individual subjects (1): approximately 590 days (Screening period of 4 weeks [28 days], treatment period of 52 weeks [365 days], and follow-up period of approximately 197 days)	Planned trial participation period for individual subjects (1): approximately 589 days (Screening period of 4 weeks [28 days], treatment period of 52 weeks [364 days], and follow-up period of approximately 197 days)
List of Abbreviations and Definitions of Terms	(Not listed)	IGS: Immunogenicity analysis set PKS: Pharmacokinetic analysis set
1.1 Pathology and Treatment of Migraine	Currently available drug therapies ... include ..., angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers.	Currently available drug therapies ... include ..., angiotensin receptor blockers, angiotensin-converting enzyme inhibitors*, and calcium channel blockers. (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.)
2.3 Dosing Rationale	Both TEV-48125 dose groups showed improvement compared to the placebo group from Week 1, and the difference from placebo group for each TEV-48125 dose group was similar. Both TEV-48125 dose groups showed improvement compared to the placebo group from Week 1, and	Both TEV-48125 dose groups showed improvement compared to the placebo group from Month 1, and the difference from placebo group for each TEV-48125 dose group was similar. Both TEV-48125 dose groups showed improvement compared to the placebo group from Month 1, and ... .
3.1 Type/Design of Trial	<u>Definition of the end of trial date for individual subject:</u> 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.	<u>Definition of the end of trial date for individual subject:</u> 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. (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.)
3.3.1 Number of Subjects and Description of Population	Up to 870 subjects who have ... 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, up to 580 subjects who have received TEV-48125 in either of the phase 2b/3 trial will undergo ADA assessment.	Up to 966 subjects who have...will be enrolled in this trial solely for the purpose of ADA assessment (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.
3.5.4 Immunogenicity	• Impact of serum anti-TEV-48125 antibodies on pharmacokinetics,	(Deleted)

Protocol Section	Before Revision	After Revision
Endpoints	efficacy, and safety	
3.7.1, Table 3.7.1-1 Table footnote for Schedule of Assessments for Subjects Receiving IMP	[c]Procedure will be performed before other assessments (eg, blood draws and administration of questionnaires).	[c]Procedure will be performed before other assessments (blood draws and administration of questionnaires).
3.7.1, Table 3.7.1-1 Table footnote for Schedule of Assessments for Subjects Receiving IMP	[k]A single blood sample for pharmacogenomic analysis will be collected at any scheduled visit during the period from V2/Baseline to V16/Follow-up from subjects who consent to DNA storage. A separate informed consent form for DNA storage must be signed by the subject.	[k]A single blood sample for pharmacogenomic analysis will be collected at any visit during the period from V2/Baseline to V16/Follow-up from subjects who consent to DNA storage. A separate informed consent form for DNA storage must be signed by the subject.
3.7.1.1.1 Visit 1/Screening (Day −28; Acceptable Window: −5 Days)	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede other scheduled assessments including blood sampling and questionnaires) • Triplicate 12-lead ECGs (should precede other scheduled assessments including blood sampling and questionnaires)	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling) • Triplicate 12-lead ECGs (should precede blood sampling)
3.7.1.2.1.1 Visit 2/Baseline (Day 1); 3.7.1.2.10 Visit 15/End of Treatment (Day 365; Acceptable Window: ± 5 Days); 3.7.1.2.11 Withdrawal (Acceptable Window: Day of Withdrawal Judgment + 7 Days)	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede other scheduled assessments including blood sampling and questionnaires) • Triplicate 12-lead ECGs (should precede other scheduled assessments including blood sampling and questionnaires)	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires) • Triplicate 12-lead ECGs (should precede blood sampling and questionnaires)
3.7.1.2.1.1 Visit 2/Baseline (Day 1); 3.7.1.2.2 Visit 3/Month 1 (Day 29; Acceptable Window: ± 5	• Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any of the scheduled visits from V2/Baseline to V16/Follow-up)	• Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at any visit from V2/Baseline to V16/Follow-up)

Protocol Section	Before Revision	After Revision
Days); 3.7.1.2.3 Visit 4/Month 2 (Day 57; Acceptable Window: ± 5 Days); 3.7.1.2.4 Visit 5/Month 3 (Day 85; Acceptable Window: ± 5 Days); 3.7.1.2.5 Visit 6/Month 4 (Day 113; Acceptable Window: ± 5 Days), Visit 10/Month 8 (Day 225; Acceptable Window: ± 5 Days), and Visit 12/Month 10 (Day 281; Acceptable Window: ± 5 Days); 3.7.1.2.6 Visit 7/Month 5 (Day 141; Acceptable Window: ± 5 Days) and Visit 13/Month 11 (Day 309; Acceptable Window: ± 5 Days); 3.7.1.2.7 Visit 8/Month 6 (Day 169; Acceptable Window: ± 5 Days) and Visit 14/Month 12 (Day 337; Acceptable Window: ± 5 Days); 3.7.1.2.8 Visit 9/Month 7		

Protocol Section	Before Revision	After Revision
(Day 197; Acceptable Window: ± 5 Days); 3.7.1.2.9 Visit 11/Month 9 (Day 253; Acceptable Window: ± 5 Days); 3.7.1.2.10 Visit 15/End of Treatment (Day 365; Acceptable Window: ± 5 Days); 3.7.1.2.11 Withdrawal (Acceptable Window: Day of Withdrawal Judgment + 7 Days); 3.7.1.3 Visit 16/Follow-up (Acceptable Window: ± 15 Days)		
3.7.1.2.2 Visit 3/Month 1 (Day 29; Acceptable Window: ±5 Days); 3.7.1.2.3 Visit 4/Month 2 (Day 57; Acceptable Window: ± 5 Days); 3.7.1.2.4 Visit 5/Month 3 (Day 85; Acceptable Window: ± 5 Days); 3.7.1.2.5 Visit 6/Month 4	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede other scheduled assessments including blood sampling and questionnaires)	• Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate) (should precede blood sampling and questionnaires)

Protocol Section	Before Revision	After Revision
(Day 113; Acceptable Window: ± 5 Days), Visit 10/Month 8 (Day 225; Acceptable Window: ± 5 Days), and Visit 12/Month 10 (Day 281; Acceptable Window: ± 5 Days); 3.7.1.2.6 Visit 7/Month 5 (Day 141; Acceptable Window: ± 5 Days) and Visit 13/Month 11 (Day 309; Acceptable Window: ± 5 Days); 3.7.1.2.7 Visit 8/Month 6 (Day 169; Acceptable Window: ± 5 Days) and Visit 14/Month 12 (Day 337; Acceptable Window: ± 5 Days); 3.7.1.2.8 Visit 9/Month 7 (Day 197; Acceptable Window: ± 5 Days); 3.7.1.2.9 Visit 11/Month 9 (Day 253; Acceptable Window: ± 5 Days)		
3.7.2.1 Electronic Headache Diary	Subjects who report headache on the previous day will answer questions about the headache (ie, occurrence of headache, duration of headache, maximum severity of headache, presence/absence of associated symptoms, and use of acute migraine medications).	Subjects who report headache on the previous day will answer questions about the headache (ie, occurrence of headache, duration of headache, maximum severity of headache, presence/absence of associated symptoms, and use of acute headache medications).

Protocol Section	Before Revision	After Revision
3.7.2.1 Electronic Headache Diary	If a subject has not entered the headache data by the end of the next day, the subject will be reminded to enter the data on the following day.	If a subject has not entered the headache data by 8 PM of the next day, the subject will be reminded to enter the data.
3.7.2.1 Electronic Headache Diary	Subjects will also record the presence or absence of photophobia, phonophobia, nausea, or vomiting, and the status of use of any acute migraine medications.	Subjects will also record the presence or absence of photophobia, phonophobia, nausea, or vomiting, and the status of use of any acute headache medications.
3.7.3.2 Clinical Laboratory Assessments Table 3.7.3.2-1 Clinical Laboratory Assessments	Creatine phosphokinase	Creatine* phosphokinase (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.)
3.7.3.5 Vital Signs	As vital signs, systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate will be measured before other assessments (eg, blood draws and questionnaires).	As vital signs, systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate will be measured before other assessments (blood draws and questionnaires).
3.7.3.5 Vital Signs	(Not included)	(however, if it is difficult to use the same position and arm due to occurrence of an AE, use of a different position or arm is acceptable.)
3.7.3.6 Twelve-lead Electrocardiography	Using 12-lead ECG equipment provided by the central laboratory selected by the sponsor, ECGs will be conducted before other assessments (eg, blood draws and questionnaires).	Using 12-lead ECG equipment provided by the central laboratory selected by the sponsor, ECGs will be conducted before other assessments (blood draws and questionnaires).
3.7.3.7 Electronic Columbia-Suicide Severity Rating Scale	Any positive findings on the eC-SSRS Since Last Visit version requires evaluation by the investigator.	Any positive findings on the eC-SSRS Baseline/Screening version or the eC-SSRS Since Last Visit version require evaluation by the investigator.
4.1 Prohibited/Restricted Medications	Subjects will be allowed to use acute migraine medication to treat acute migraine attacks, as needed, but will not be allowed to use it as preventive medication.	Subjects will be allowed to use acute headache medication only at the time of occurrence of a headache attack, as needed, but will not be allowed to use it as preventive medication.
4.1.1 Prohibited Medications (Preventive Migraine Medications), Table 4.1.1-1 List of Prohibited Concomitant Medications (Preventive Migraine Medications)	Angiotensin receptor blockers	Angiotensin receptor blockers/ angiotensin-converting enzyme inhibitors
4.2 Prohibited Concomitant	Use of an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for treatment will	Use of an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for treating

Protocol Section	Before Revision	After Revision
Therapies	be prohibited.	migraine will be prohibited.
5.1 Definitions	• Any ophthalmic AE of at least moderate severity	• Any ophthalmic AE of at least moderate severity (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.)
6.1.1 Pharmacokinetic Analysis Set	(No outline numbering)	(1) Pharmacokinetic Analysis Set 1 (PKS 1)
6.1.1 Pharmacokinetic Analysis Set	The pharmacokinetic analysis set will include all subjects in whom at least 1 dose of IMP is administered, and effective plasma drug concentration is measured for at least 1 time point after IMP dosing. However, subjects whose entire data are rejected in Section 6.1.2 (3), Analysis Method 1), will be excluded from the pharmacokinetic analysis set.	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 those who have rolled over to the present trial, those who received at least one dose of IMP in Trial 406-102-00002 and in whom an effective plasma drug concentration is measured for at least one postdose time point in the present trial will be included.
6.1.1 Pharmacokinetic Analysis Set	(Not included)	(2) Pharmacokinetic Analysis Set 2 (PKS 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 IMP in either the present trial, Trial 406-102-00001, or Trial 406-102-00002 and in whom an effective plasma drug concentration is measured for at least one postdose time point in the present trial will be included.
6.1.2 Pharmacokinetic Analysis Set (2) Dataset for Analysis	Pharmacokinetic analysis set	Pharmacokinetic analysis sets (PKS 1 and PKS 2)
6.1.2 Pharmacokinetic Analysis Set (3) Analysis Method	2) Concerning Section 6.1.2 (1), Endpoint, descriptive statistics will be calculated by treatment group for each blood sampling time point.	2) Concerning Section 6.1.2 (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.
6.2.1 Immunogenicity Analysis Set	(No outline numbering)	(1) Immunogenicity Analysis Set 1 (IGS 1)
6.2.1	The immunogenicity analysis set will	Of the subjects who were enrolled in the

Protocol Section	Before Revision	After Revision
Immunogenicity Analysis Set	include all subjects in whom at least 1 dose of IMP is administered in either the phase 2b/3 trials or this trial, and serum ADA is measured for at least 1 time point after IMP dosing.	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 IMP in Trial 406-102-00002 and in whom serum ADA is measured for at least one postdose time point in the present trial will be included.
6.2.1 Immunogenicity Analysis Set	(Not included)	(2) 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 IMP in either the present trial, Trial 406-102-00001, or Trial 406-102-00002 and in whom serum ADA is measured for at least one post-dose time point in the present trial will be included.
6.2.2 Immunogenicity Analysis	Summary of immunogenicity results in the immunogenicity analysis set will be provided, and the incidence of immunogenicity expression will be calculated. The impact of immunogenicity on the pharmacokinetics, efficacy, and safety will be evaluated.	Summary of immunogenicity results will be provided, and the incidence of immunogenicity expression will be calculated separately for IGS 1 and IGS 2.
7.1 Sample Size	..., up to 870 subjects who ... will be enrolled in this trial. ... . Therefore, ADA assessment will be performed in up to 580 subjects (approximately 360 subjects and 220 subjects who have received TEV-48125 in Trial 406-102-00001 and Trial 406-102-00002, respectively).	..., up to 966 subjects who ... will be enrolled 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).
7.4 Analysis of Demographic and Baseline Characteristics	For demographic and baseline characteristics of subjects with CM or EM and of each treatment group, either descriptive statistics will be calculated or frequency distribution will be obtained according to the nature of characteristics, using the RS as the analysis set.	For demographic and baseline characteristics, either descriptive statistics will be calculated or frequency distribution will be obtained overall and by treatment group according to the nature of characteristics using RS as the analysis set.
7.5.1 Adverse Events	The incidence of the following events will be summarized by disease subtype (CM or EM) and by treatment group:	The incidence of the following events will be summarized overall and by treatment group:
7.5.2 Clinical Laboratory Data	For clinical laboratory data and changes from baseline at each time point (including the final evaluation),	For clinical laboratory data and changes from baseline at each time point (including the final evaluation),

Protocol Section	Before Revision	After Revision
	descriptive statistics will be calculated by disease subtype (CM or EM) and by treatment group. For the numbers of subjects with clinical laboratory data meeting the criteria for potentially clinically significant values, frequency distributions will be obtained by disease subtype (CM or EM) and by treatment group.	descriptive statistics will be calculated overall and by treatment group. For the numbers of subjects with clinical laboratory data meeting the criteria for potentially clinically significant values, frequency distributions will be obtained overall and by treatment group.
7.5.3 Vital Signs and Weight Data	For vital sign and weight measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated by disease subtype (CM or EM) and by treatment group.	For vital sign and weight measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated overall and by treatment group.
7.5.4 Twelve-lead Electrocardiogram Data	For ECG measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated by disease subtype (CM or EM) and by treatment group. For the results of assessments (normal or abnormal), a shift table from baseline will be displayed.	For ECG measurements and changes from baseline at each time point (including the final evaluation), descriptive statistics will be calculated overall and by treatment group. For the results of assessments, a shift table from baseline will be displayed.
7.5.5 Injection Site Reactions	For severities of the injection site reactions (erythema, induration, ecchymosis, and pain), frequency distributions will be obtained by disease subtype (CM or EM) and by treatment group.	For severities of the injection site reactions (erythema, induration, ecchymosis, and pain), frequency distributions will be obtained overall and by treatment group.
7.6 Efficacy Analysis	Efficacy data will be summarized by disease subtype (CM or EM) and by treatment group, using the FAS as the analysis set.	Efficacy data will be summarized by treatment group, using the FAS as the analysis set.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Amendment Number: 3

Issue Date: 28 Feb 2019

PURPOSE:

To reflect the extension of the trial duration

BACKGROUND:

Revisions were made because the trial period was extended.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
Protocol Synopsis, Trial Duration	Overall trial period: Aug 2017 through Feb 2020 (planned)	Overall trial period: Aug 2017 through Jun 2020 (planned)

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Amendment Number: 4

Issue Date: 08 Jul 2019

PURPOSE:

To reflect the extension of the trial duration and to achieve clearer and more precise wording and correct errors in the text.

BACKGROUND:

Revisions were made because the trial period was extended. Revisions were also made because unclear wording and errors in the text were found. Inconsistencies in descriptions between the two phase 2b/3 trials (Trials 406-102-00001 and 406-102-00002) were also resolved.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
Protocol Synopsis, Trial Duration	Overall trial period: Aug 2017 through Jun 2020 (planned)	Overall trial period: Aug 2017 through Sep 2020 (planned)
5.3 Immediately Reportable Events (IREs)	An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is not the AE page of the CRF.)	An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is not the AE page of the CRF.) When sending an IRE form by e-mail, etc, sufficient care and attention must be taken to protect subject privacy.
7.2 Analysis Sets	• Full analysis set (FAS): Newly enrolled subjects in the RS who receive the IMP at least once	• Full analysis set (FAS): Newly enrolled subjects in the SS for whom electronic headache diary efficacy assessment data at baseline and after the first dose of IMP are available
11 Ethics and Responsibility	Further, in preparing and handling CRFs, the investigator and their staff will	Further, in preparing and handling CRFs, IRE forms, etc., the investigator and their staff will ....
15 References Reference No. 18	Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the quality standards subcommittee of american academy of neurology. Neurology. 2000;55:754-62.	Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the quality standards subcommittee of American Academy of Neurology. Neurology. 2000;55:754-62.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.