CLINICAL STUDY PROTOCOL

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

NCT Number: NCT03303079

PRT NO.: 406-102-00001

Version Date: 08 July 2019 (Version 5.0)

<English Translation of Japanese Original>

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
TEV-48125

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Protocol No. 406-102-00001

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	2b/3
Sponsor:	Otsuka Pharmaceutical Co., Ltd.
Immediately Reportable Event:	PAREXEL International Global Medical Services, Pharmacovigilance E-mail: IRE_406-102-00001@otsuka.jp
Issue Date (Original):	10 Aug 2017
Amendment 1:	30 Nov 2017
Amendment 2:	18 Jun 2018
Amendment 3:	28 Feb 2019
Amendment 4:	08 Jul 2019
Version No.:	5.0 (English translation, 06 Aug 2019)

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Co., Ltd. Name of Investigational Medicinal Product: TEV-48125	Protocol No.: 406-102-00001
Protocol Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial Evaluating the Efficacy and Safety of Subcutaneous Administration of TEV-48125 for the Preventive Treatment of Chronic Migraine
Clinical Phase/Trial Type:	Phase 2b/3 confirmatory trial
Treatment Indication:	Preventive treatment of chronic migraine (CM)
Objectives:	To evaluate the efficacy and safety of subcutaneous (SC) administration of TEV-48125 [monthly TEV-48125 225 mg (loading dose only: 675 mg) and TEV-48125 675 mg once over a period of 3 months] compared with placebo for preventive treatment in CM patients
Trial Design:	Multicenter, randomized, double-blind, placebo-controlled, parallel group trial
Subject Population:	540 males or females (180 per group, a total of 3 groups) with CM aged 18 to 70 years, inclusive (the plan is to enroll at least approximately half of the subjects in Japan)
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 in baseline information collected during the 28-day screening period: – Headache occurring on ≥ 15 days – Fulfilling any of the following on ≥ 8 days: • 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 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 1 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. • 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: • Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after use for at least 3 months at accepted migraine therapeutic doses: – Cluster A: topiramate, divalproex sodium and sodium valproate – Cluster B: lomerizine, flunarizine and pizotifen – Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine – Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol • Patient suffers from unremitting headaches, defined as having headaches for more than 80% of the time that he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if the patient has headaches 80% or less of the time they are awake on most days. • Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator
Trial Sites:	Approximately 60 sites (52 sites in Japan and 8 sites in South Korea) (planned)
Investigational Medicinal Products, Dose, Dosage Regimen, Treatment Period, Formulation, Mode of Administration:	TEV-48125 or placebo will be subcutaneously administered once monthly for 3 months for a total of 3 doses. Monthly dosing refers to dosing every 4 weeks (28 days). The investigational medicinal product (IMP) will be administered by trial personnel responsible for administration of injections.

	• TEV-48125 675/225/225 mg group: Subjects will receive 675 mg of TEV-48125 as 3 active injections (225 mg/1.5 mL) at Visit (V) 2/Baseline and 225 mg of TEV-48125 as a single active injection (225 mg/1.5 mL) at V3/Month 1 and V4/Month 2. • TEV-48125 675 mg/placebo/placebo group: Subjects will receive 675 mg of TEV-48125 as 3 active injections (225 mg/1.5 mL) at V2/Baseline and placebo as a single 1.5-mL injection at V3/Month 1 and V4/Month 2. • Placebo group: Subjects will receive three 1.5-mL placebo injections at V2/Baseline and a single 1.5-mL placebo injection at V3/Month 1 and V4/Month 2.
Trial Assessments:	Efficacy: Electronic headache diary, 6-Item Headache Impact Test (HIT-6), 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, and Work Productivity and Activity Impairment (WPAI) questionnaire Safety: Adverse events, clinical laboratory tests, physical examination, weight, vital signs, 12-lead electrocardiograms, electronic Columbia-Suicide Severity Rating Scale (eC-SSRS), injection site reaction, urine human chorionic gonadotropin (HCG) test (women of childbearing potential [WOCBP] only), and concomitant medications and therapies Pharmacokinetics: Blood sampling for measurement of plasma drug concentrations Screening/Other: Height, prior medications and therapies, serum HCG test (WOCBP only), follicle-stimulating hormone test (women at least 12 months postmenopausal only), blood sampling for serum antidrug antibody assessment, blood sampling for pharmacogenomic analysis, and blood and urine sampling for biomarker analysis
Criteria for Evaluation:	**Primary Endpoint:** Mean change from baseline in the monthly (28-day) average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP **Secondary Endpoints:** • Mean change from baseline in the monthly average number of migraine days during the 12-week period after the first dose of IMP

	• Proportion of subjects reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP • Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP • Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications • Mean change from baseline in disability score, as measured by the HIT-6, at 4 weeks after the final (third) dose of IMP
Statistical Methods:	Analysis of Primary Endpoint: The primary endpoint will be analyzed in the full analysis set (FAS) using an analysis of covariance model. The model will include treatment group, sex, country, and baseline preventive medication use as fixed effects and the baseline number of headache days of at least moderate severity and years since onset of migraines as covariates. Two-sided 95% confidence intervals and p-values will be constructed for the least squares mean differences between each TEV-48125 group and the placebo group. Multiplicity problems will be avoided using a closed testing procedure. If superiority of the TEV-48125 675/225/225 mg group to the placebo group is confirmed at a two-sided significance level of 0.05, then the TEV-48125 675 mg/placebo/placebo group vs the placebo group will be tested at a two-sided significance level of 0.05. Rationale for Target Sample Size: In a phase 2b trial in CM patients (Trial LBR-101-021), concerning the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP, the difference between the TEV-48125 675/225/225 mg group and the placebo group was 1.7 days and the standard deviation was 4.9 days. On the assumption that this trial will also yield a similar result to the phase 2b trial (Trial LBR-101-021), a sample size of 176 subjects per group gives more than 90% power for the trial to succeed at a significance level of 0.05 (two-sided). Based on the above and taking into account a small percentage of subjects who

	may be excluded from the FAS, the target sample size was determined to be 180 subjects per group and 540 subjects as the overall total included in the trial.
Trial Duration:	Overall trial period: Aug 2017 through Mar 2020 (planned) Trial participation period for individual subjects: approximately 112 days (Screening period of 4 weeks [28 days] and double-blind treatment period of 12 weeks [84 days])

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Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BMI	Body mass index
CBC	Complete blood count
CDMS	Clinical data management system
CFR	Code of Federal Regulations
CGRP	Calcitonin gene-related peptide
CM	Chronic migraine
C_{max}	Maximum (peak) plasma concentration of the drug
CRF	Case report form
CRO	Clinical Research Organization
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
EOT	End-of-treatment (visit)
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
ES	Enrolled set
EU	European Union
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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3 beta	International Classification of Headache Disorders, third edition (beta version)
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	International Headache Society
IMP	Investigational medicinal product
INR	International normalization ratio
IRB	Institutional review board
IRE	Immediately reportable event
IRT	Interactive response technology

Abbreviation	Definition
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MSQOL	Migraine-Specific Quality of Life
NOAEL	No-observed-adverse-effect level
PE	Physical examination
PEF	Peak expiratory flow
PGIC	Patient Global Impression of Change
PHQ-2	2-Item Patient Health Questionnaire
PHQ-9	9-Item Patient Health Questionnaire
PMDA	Pharmaceuticals and Medical Devices Agency
PQC	Product quality complaint
RBC	Red blood cell
RNA	Ribonucleic acid
RS	Randomized set
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
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
US or USA	United States or United States of America
V	Visit
WBC	White blood cell
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 (of moderate to severe severity, unilateral, and/or pulsating) 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 and 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); and 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 improvement 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 included 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 or 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

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 have 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 and 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 in healthy Japanese and Caucasian subjects (Trial TV48125-PK-10078) have demonstrated similarities in the safety profile of TEV-48125 between the 2 populations, and Japanese patients are enrolled in ongoing multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050), which began ahead of this trial. It is considered necessary to investigate recommended doses and regimens in Japanese patients by assessing the response in this population to 2 different doses and regimens and to demonstrate that the efficacy and safety of TEV-48125 in Japanese patients is similar to the efficacy and safety observed in

the multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050), which warrants the implementation of this clinical trial.

This trial will be conducted in Japan and South Korea. Although no TEV-48125 data from Koreans are available, an absence of ethnicity difference in CGRP polymorphism and key pharmacological properties of TEV-48125 suggest that TEV-48125 is less susceptible to intrinsic factors. In addition, in the light of minimal differences between Japan and South Korea in diagnostic criteria, epidemiology, and therapeutic approach, TEV-48125 is unlikely to be affected by extrinsic factors. Based on the above, the pharmacokinetics, safety, and efficacy of TEV-48125 is expected to be virtually the same between Japanese and Korean populations, and the conduct of this trial in both Japanese and Korean patients to assess the efficacy and safety of TEV-48125 should be appropriate.

Prior to the implementation of this trial, the sponsor held Additional Consultation (Other Than Orphan Drugs) and Consultation After Face-to-face Meeting with the Pharmaceuticals and Medical Devices Agency (PMDA) on 01 Nov 2016 and 16 Mar 2017, respectively, and received the PMDA's advice on the appropriateness of conducting a Japanese and Korean collaborative clinical trial, efficacy endpoints, dose selection, sample size, and other issues.

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[14] 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).

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.

The doses and dosing regimens of SC TEV-48125 in this trial are mainly based on relevant data including the results from phase 2b trials (Trials LBR-1012-021 and LBR-101-022) that assessed efficacy, safety, and regimens in patients with migraine. The doses and dosing regimens used in phase 2b trials (Trials LBR-101-021 and LBR-101-022) 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. Based on these findings, the lower dose of TEV-48125 used in the phase 2b trial (Trial LBR-101-021) was considered appropriate for this trial. In the lower dose group in the phase 2b trial (Trial LBR-101-021), a loading dose of 675 mg was used despite the lowest effective dose of 225 mg. Since early appropriate preventive treatment for CM is recommended,[11] 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. Therefore, in this phase 2b/3 trial in CM patients (Trial 406-102-00001), 225 mg of TEV-48125 will be administered once monthly (except for a loading dose of 675 mg) in one of 2 TEV-48125 dose groups to evaluate the efficacy and safety in Japanese subjects. In the other TEV-48125 dose group, 675 mg of TEV-48125 will be administered once in 3 months to determine how different doses and dosing regimens may affect the efficacy of TEV-48125 in Japanese subjects.

This trial is designed to be placebo-controlled in consideration of the objective of the trial and the trial design recommended by the Classification Committee of the International Headache Society (IHS) guidelines for controlled trials of prophylactic treatment of CM

in adults[15] and the Classification Committee of IHS recommendations for controlled trials of migraine prophylactic drugs.[16]

2.4 Rationale for Treatment Period

The treatment period was determined in consideration of the treatment period recommended by the Classification Committee of IHS recommendations for controlled trials of migraine prophylactic drugs.[16]

2.5 Trial Objective

To evaluate the efficacy and safety of SC administration of TEV-48125 (monthly TEV-48125 225 mg [loading dose only: 675 mg] and TEV-48125 675 mg once over a period of 3 months) compared with placebo for preventive treatment in CM patients.

3 Trial Design

3.1 Type/Design of Trial

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

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

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

The trial includes the following treatment groups.

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

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

Definition of the end of trial date for individual subject:

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

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

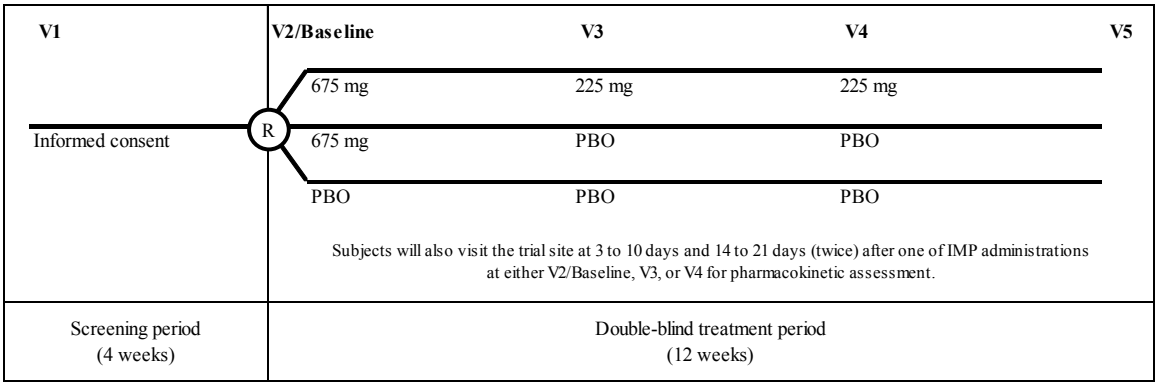


Figure 3.1-1 Trial Design Schematic

PBO = placebo; R = randomization.

3.2 Trial Treatments

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

The dosing regimens for treatment groups are shown below.

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

At the time of each visit, the 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.[17] 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 locations will be recorded for each dosing visit (V2/Baseline, V3/Month 1, and V4/Month 2).

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

A total of 540 male or female (180 per group, a total of 3 groups) with CM aged 18 to 70 years, inclusive, will be enrolled in the trial. The plan is to enroll at least approximately half of the subjects in Japan. The enrollment procedure will be continued until the number of enrolled subjects reaches 540.

Continued concomitant use of some preventive migraine medications (see Table 4.1.2-1) may be permitted, so long as a stable dose and regimen have been maintained for at least 2 consecutive months prior to informed consent, in which case the subject will be allowed to continue using no more than 1 preventive medication. However, the total

number of subjects receiving concomitant preventive medication during the trial will not exceed 30% of the total sample size of the trial.

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 across this trial (CM patients; hereinafter the same applies) and Trial 406-102-00002 (EM patients; hereinafter the same applies) in the chronological order informed consent is obtained in, starting at 10001. Following screening, subjects who meet the eligibility criteria for either this trial or Trial 406-102-00002 will be randomized into the trial for which they are eligible. Subjects who fail to meet the eligibility criteria for both this trial and Trial 406-102-00002 after providing their consent to participate in both this trial and Trial 406-102-00002 or only in this trial will be handled as screen failures for this trial. 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 written information for subjects and ICF will comply with the ICH (International Conference on Harmonisation) Good Clinical Practice (GCP) Guideline[18] 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 a qualified 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 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.

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 International Classification of The 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

Table 3.4.2-1	Inclusion Criteria
5	Patient fulfills all the following criteria for CM in baseline information collected during the 28-day screening period: • Headache occurring on ≥ 15 days • Fulfilling any of the following on ≥ 8 days: – 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 1 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.
7	Body mass index (BMI) of 17.5 to 37.5 and total weight between 35.0 and 120.0 kg, inclusive
8	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	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 CM.
6: This criterion is set to appropriately evaluate efficacy. Since the guidelines developed by the Headache Consortium[4,19] recommend preventive therapies for all CM patients having frequent headache and severe impairment, the use of 1 preventive medication 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.

Table 3.4.3-1	Exclusion Criteria
1	Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face, or neck during the 4 months prior to giving informed consent.
2	Patient is using medications containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine, butalbital/paracetamol/caffeine, or any other combination containing butalbital) on more than 4 days per month for the treatment of migraine or for any other reason.

Table 3.4.3-1 Exclusion Criteria	
3	Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after use for at least 3 months at accepted migraine therapeutic doses: • Cluster A: topiramate, divalproex sodium and sodium valproate • Cluster B: lomerizine, flunarizine and pizotifen • Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine • Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol
4	Patient has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine during the 2 months prior to giving informed consent.
5	Patient suffers from unremitting headaches, defined as having headaches for more than 80% of the time that he/she is awake, and less than 4 days without headache per month. Daily headache is acceptable if the patient has headaches 80% or less of the time they are awake on most days.
6	Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator
7	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
8	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
9	Known infection or history of human immunodeficiency virus (HIV), tuberculosis, or hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
10	Past or current history of cancer in the past 5 years, except for appropriately treated skin carcinoma other than malignant melanoma
11	History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
12	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
13	Any prior exposure to a monoclonal antibody targeting the CGRP pathway (such as AMG334, ALD304, LY2951742, or TEV-48125)
14	Any finding in the screening or baseline 12-lead ECG considered clinically significant in the judgment of the investigator
15	Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including in chemistry, hematology, coagulation, and urinalysis test values
16	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
17	Serum creatinine more than 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease at screening
18	History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years
19	Female patient who is nursing at the time informed consent is obtained or who tests positive in pregnancy test at screening or baseline

Table 3.4.3-1 Exclusion Criteria	
20	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] level above 35 U/L).
21	The patient cannot participate or successfully complete the trial for other reasons in the opinion of the investigator.

[Rationales for exclusion criteria]
1 through 5: These criteria are set to appropriately evaluate efficacy.
6 through 10, 12, 18, and 21: These criteria are set to appropriately evaluate efficacy and safety.
11 and 14 to 17: These criteria are set to appropriately evaluate the safety.
13: This criterion is set to avoid potential influence on the blindness and safety.
19 and 20: These criteria are set because the safety of the IMP in pregnant or nursing females has not been established.

Screen failure subjects may be rescreened if prior agreement is obtained from the sponsor. If a subject is to be rescreened, informed consent must be newly obtained, and a new subject identification number must be assigned to the subject prior to the rescreening examination.

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the mean change from baseline in the monthly (28-day) average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP.

This is consistent with the primary endpoint recommended by the Classification Committee of IHS guidelines for controlled trials of prophylactic treatment of CM in adults.[15]

3.5.2 Secondary Endpoints

3.5.2.1 Efficacy Endpoints

The efficacy endpoints for this trial are as follows:

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

- Proportion of subjects reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP
- Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
- Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications
- Mean change from baseline in disability score, as measured by the 6-Item Headache Impact Test (HIT-6), at 4 weeks after the final (third) dose of IMP

3.5.2.2 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)

3.5.3 Exploratory Endpoints

The exploratory 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 headache hours
- Number of days with use of any acute headache medications
- Number of days with nausea or vomiting
- Number of days with photophobia or phonophobia
- Migraine-Specific Quality of Life (MSQOL)
- EuroQol-5 Dimension, 5 response level version (EQ-5D-5L)
- 2-Item Patient Health Questionnaire (PHQ-2) and 9-Item Patient Health Questionnaire (PHQ-9)

- Work Productivity and Activity Impairment (WPAI)
- Patient Global Impression of Change (PGIC)

3.5.4 Pharmacokinetic Endpoint

The pharmacokinetic endpoint for this trial is as follows:

- Plasma TEV-48125 concentrations

3.5.5 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

In this randomized, double-blind trial, subjects will be randomly assigned with stratification based on sex, country, and use of preventive migraine medication at V2/Baseline to 3 groups in a 1:1:1 ratio. Further details of randomization will be presented in the Subject Randomization Code Manual.

In this double-blind trial, all subjects and investigators will remain blinded to the subject randomization code. Any party on the sponsor's side involved in the trial, including contract research organizations (CROs) but excluding drug concentration measurement facilities and ADA measurement facilities, will also remain blinded to the subject randomization code during the trial period. Prior to trial commencement, the indistinguishability of IMP will be confirmed by the sponsor. The emergency code will be controlled by the IRT until the end of the trial. In the event that a subject experiences a medical emergency or the safety of a subject needs to be confirmed immediately and knowledge of the IMP assignment code is considered essential to adequately treat the subject, the emergency code for the subject may be broken (see Section 5.7, Procedure for Breaking the Blind). However, the results of ADA and pharmacokinetic assessments should not be disclosed until code breaking at the end of the trial. ADA and pharmacokinetics will be assessed by specified facilities, not by laboratories at trial sites.

3.7 Trial Procedures

Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

Procedures and Assessments	Period	Screening Period	Double-blind Treatment Period					
	Visit	V1/Screening	V2/Baseline	V3/Month 1	V4/Month 2	Additional visits for PK[b]	V5/End of treatment (Month 3)	Withdrawal
	Study Day	Day -28	Day 1	Day 29	Day 57		Day 85	
	Acceptable window	-3		±3	±3		±3	Day of withdrawal decision + 7
Informed consent		X[a]						
Informed consent to DNA storage (voluntary)		X						
Demographics		X						
Eligibility assessment		X	X					
Randomization			X					
IMP administration			X	X	X			
Injection site response assessment[c]			X	X	X			
Physical examination		X	X	X	X		X	
Height		X						
Weight		X	X				X	
12-Lead ECG[d,e]		X	X			X	X	
Vital signs[d] (systolic and diastolic pressure, pulse rate, temperature, respiratory rate)		X	X	X	X		X	
Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis)		X	X	X	X		X	
Serum HCG test[f]		X						
Urine HCG test[f]			X	X	X		X	
FSH test[g]		X						
Adverse events[h]		←	—	—	—	—	—	→
Preventive migraine medication inquiry			X					
Medication and therapy inquiry		←	—	—	—	—	—	→
eC-SSRS[i]			X	X	X		X	
Provide electronic headache diary device[j]		X						
Complete electronic headache diary entries[k]		X	—	—	—	—	X	
Review electronic headache diary			X	X	X		X	
Return electronic headache diary device							X	
Blood samples for plasma drug concentration[l]			X	X	X	X	X	
Blood samples for serum ADA assessment[m]			X	X			X	
Blood samples for pharmacogenomic analysis[n]			X					
Blood and urine samples for biomarker analysis			X		X		X	
HIT-6			X				X	
PHQ-2/PHQ-9[o]			X				X	
MSQOL questionnaire			X	X	X		X	
EQ-5D-5L questionnaire			X				X	
PGIC scale				X	X		X	
WPAI questionnaire			X				X	

HCG = serum human chorionic gonadotropin.

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

[b] A total of 2 visits will be performed at 3 to 10 days and at 14 to 21 days postdose at V2/Baseline, V3/Month 1, or V4/Month 2.

[c] Injection site reaction will be assessed 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.

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

[e] 12-Lead ECGs will be performed in triplicate.

[f] Women of childbearing potential only.

[g] Women at least 12 months postmenopausal only.

[h] Inquiries about AEs will be made before and after IMP administration. Postdose inquiries will be made before the subject leaves the trial site.

[i] 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.

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

[k] Subjects will complete electronic headache diary entries about the previous day daily beginning at V1/Screening through V5/End of treatment or the day before withdrawal.

[l] Blood samples for plasma drug concentration determination will be collected prior to dosing at V2/Baseline, V3/Month 1, and V4/Month 2.

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

[n] A single blood sample for pharmacogenomic analysis will be collected at V2/Baseline or any visit thereafter from subjects who consent to DNA storage. A separate informed consent form for DNA storage must be signed by the subject.

[o] 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.

3.7.1 Schedule of Assessments

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: −3 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)
- Triplicate 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 Double-blind Treatment Period

The double-blind treatment period begins at V2/Baseline and ends at V5/End of treatment or the time of withdrawal.

Each day during the double-blind treatment period, subjects will enter headache information about the previous day into the electronic headache diary.

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.

- Visit date
- Result of eligibility assessment
- Use of preventive migraine medications
- Randomization
  - Date of randomization
  - Randomization number
- Electronic headache diary
- 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)
- 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 V2/Baseline or any visit thereafter)
- HIT-6
- PHQ-2/PHQ-9 (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.)
- 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 will subcutaneously receive the IMP (see Section 3.2, Trial Treatments). 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. Trial personnel will enter subject information in the IRT. Eligible subjects will be randomly assigned with stratification based on sex, country, and use of preventive migraine medication at V2/Baseline (yes, no) to one of the following 3 groups:

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

3.7.1.2.2 Visit 3/Month 1 (Day 29; Acceptable Window: ± 3 Days) and Visit 4/Month 2 (Day 57; Acceptable Window: ± 3 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
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine HCG test (WOCBP only)
- Blood sampling for serum ADA assessment (V3/Month 1 only)
- Blood and urine sampling for biomarker assessment (V4/Month 2 only)
- Blood sampling for plasma drug concentration determination
- Blood sampling for pharmacogenomic assessment (only subjects who consent to DNA storage) (will be performed at V2/Baseline or any visit thereafter)
- MSQOL questionnaire
- PGIC scale
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs

After the above predose assessments/tests/observations are completed, subjects will subcutaneously receive IMP (see Section 3.2, Trial Treatments). 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 5/End of Treatment (Day 85; Acceptable Window: ± 3 Days) and Withdrawal (Acceptable Window: Day of Withdrawal Decision + 7 Days)

As the final evaluation (V5/End of treatment), the following assessments/tests/observations will be performed. 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.

Subjects will be offered the opportunity to enter the long-term trial for the purpose of evaluating ADA at 225 days (approximate equivalent of 5 half-lives) after the final dose of IMP (V4/Month 2) in this trial.

- 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)
- 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)
- 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 V2/Baseline or any visit thereafter)
- HIT-6
- PHQ-2/PHQ-9 (Subjects will respond first to the PHQ-2. They will respond to questions 3 through 9 [unique questions] of the PHQ-9 only if the PHQ-2 is positive.)
- MSQOL questionnaire

- EQ-5D-5L questionnaire
- WPAI questionnaire
- PGIC scale
- eC-SSRS (Since Last Visit version)
- Concomitant medications and therapies
- AEs
- Participation in the long-term trial (yes, no)

3.7.1.3 Two Additional Visits for Pharmacokinetic Analysis (3 to 10 Days and 14 to 21 Days After One of the IMP Administrations at Either Visit 2/Baseline, Visit 3/Month 1, or Visit 4/Month 2)

At 2 additional visits at 3 to 10 days and at 14 to 21 days after one of the IMP administrations at either V2/Baseline, V3/Month 1, or V4/Month 2, the following assessments/tests/observations will be performed and recorded on the CRF.

- Blood sampling for plasma drug concentration determination
- Triplicate 12-lead ECGs (should precede blood sampling)
- 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.

3.7.2 Efficacy Assessments

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 3.7.2.7) 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 missed 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 will assess the impact of headache on social functioning, role functioning, vitality, cognitive functioning, and psychological distress, using the HIT-6.

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

The PHQ-2 and PHQ-9 will be completed by subjects for the detection and monitoring of 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.

3.7.2.4 Migraine-Specific Quality of Life Questionnaire

Using the MSQOL questionnaire, subjects will 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.

3.7.2.5 EuroQol-5 Dimension, 5 Response Level Version Questionnaire

Using the EQ-5D-5L questionnaire, subjects will 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.

3.7.2.6 Patient Global Impression of Change Scale

Using the PGIC scale, subjects will 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.

3.7.2.7 Work Productivity and Activity Impairment Questionnaire

Subjects will assess the overall effect of health on productivity at work and daily activities during the past 7 days prior to the assessment day using a generic version of the WPAI questionnaire, and the specific health problems version of the WPAI questionnaire 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 62 mL (approximately 86 mL for Korean subjects).

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 normalized 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, temperature, and respiratory rate will be measured before other assessments (blood draws and questionnaires). Before blood pressure and pulse rate 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, systolic and diastolic blood pressures (integer; mmHg), pulse rate (integer; beats/min), 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. The ECGs will be performed in triplicate within several 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

The eC-SSRS will be used to assess the subject's suicidal ideation (severity and intensity) and suicidal behavior.[20] 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 date for individual subject. 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
- V3/Month 1 (Day 29; acceptable window: ± 3 days): Predose
- V4/Month 2 (Day 57; acceptable window: ± 3 days): Predose
- V5/End of treatment (Day 85; acceptable window: ± 3 days)
- V2/Baseline, V3/Month 1, or V4/Month 2: 3 to 10 days and 14 to 21 days postdose at V2/Baseline, V3/Month 1, or V4/Month 2
- Withdrawal (acceptable window: day of withdrawal decision + 7 days)

As immunogenicity will be assessed at 225 days (acceptable window: ± 15 days, the approximate equivalent of 5 half-lives) after the final dose of IMP in this trial, pharmacokinetics will also be assessed at the same time. Blood collection for this time point will be performed in the long-term trial.

(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 the TEV-48125 group 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 after unblinding.

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

It was determined to collect blood at 1 time point before the first dose and a total of 3 time points 28 days after each of 3 doses to collect trough values at 28 days after each dose so that plasma concentrations of TEV-48125 following repeated administration of TEV-48125 can be evaluated. In order to obtain information on the absorption phase and early elimination phase in patient groups in addition to the trough values stated above, it was also determined to collect blood at 3 to 10 days and 14 to 21 days after any of the 3 doses of the IMP. Consequently, blood will be collected from each subject at a total of 6 time points.

Because ADA will be assessed during the long-term trial at 225 days after the final dose of IMP in this trial (when plasma TEV-48125 concentrations are considered to be sufficiently decreased), one blood sampling time point is set in the long-term trial so that pharmacokinetics can also be assessed at the same time.

3.7.4.2 Immunogenicity

(1) Timing of Blood Sampling

- V2/Baseline (Day 1): Predose
- V3/Month 1 (Day 29; acceptable window: ± 3 days): Predose
- V5/End of treatment (Day 85; acceptable window: ± 3 days)
- Withdrawal (acceptable window: day of withdrawal decision + 7 days)
- Upon observation of any severe hypersensitivity reaction (eg, anaphylaxis).

Immunogenicity will also be assessed at 225 days (acceptable window: ± 15 days, the approximate equivalent of 5 half-lives) after the final dose of the IMP in this trial. Blood collection for this time point will be performed in the long-term trial.

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 in the TEV-48125 group using a validated measurement method. The ADA measurement

facility will submit the electronic file of the results of ADA measurements to the sponsor after unblinding.

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, 1 time point 28 days after the first dose when an increase in IgG is expected to occur, and 1 time point 28 days after the final dose of monthly IMP administration (equivalent to 28 days after the final dose of IMP administered once monthly and 12 weeks after the final dose of IMP administered once over a period of 3 months) in consideration of assessment time points recommended in the Food and Drug Administration Guidance[21] (approximately 30 days after the final dose) and the European Medicines Agency Guidelines[22] (at least 4 weeks after the final dose). Consequently, blood will be collected from each subject at a total of 3 time points. In consideration of the potential effect of residual drug in the blood on ADA assessment, blood will also be sampled during the long-term trial at 225 days after the final dose of IMP in this trial when plasma TEV-48125 concentrations are considered to be sufficiently decreased.

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. 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 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
- V4/Month 2 (Day 57; acceptable window: ± 3 days): Predose
- V5/End of treatment (Day 85; acceptable window: ± 3 days)
- Withdrawal (acceptable window: day of withdrawal decision + 7 days)

(3) Sampling and Storage Methods

Blood and urine will be collected at the scheduled time points to obtain biomarker samples (serum, plasma, 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 trial completion date or discontinuation date that will be recorded on the completion of trial page of the CRF prepared for the last subject who completes or is withdrawn from the trial (for the subject who is lost to follow up, the date of his/her last visit/contact or the date of the last attempt to contact him/her recorded on the follow-up page) (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 3.7.1.2.3, Visit 5/End of Treatment (Day 85; Acceptable Window: ± 3 Days) and Withdrawal (Acceptable Window: Day of Withdrawal Decision + 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 subject's legally acceptable representative if the subject is a minor) 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 their 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

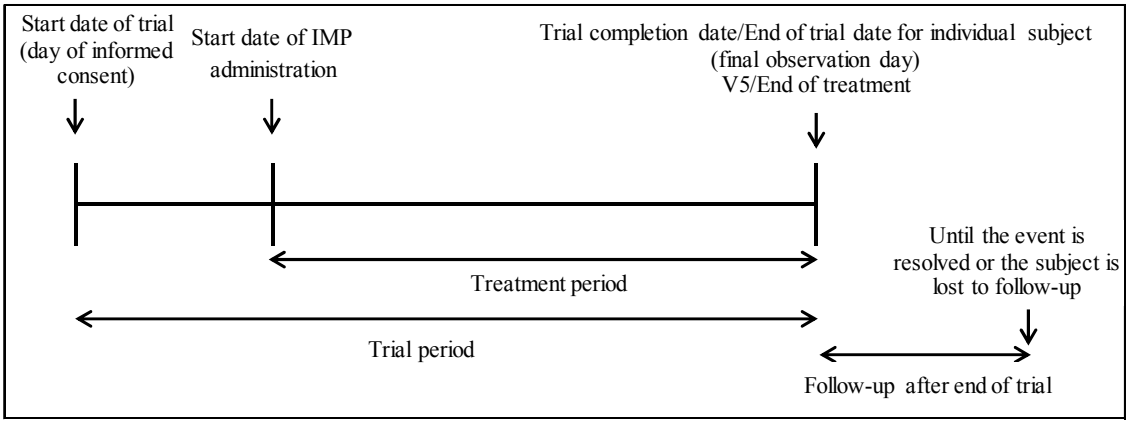
A screen failure subject in this trial is one from whom written informed consent is obtained for only this trial in patients with CM or for both this trial and Trial 406-102-00002 in patients with EM, but who is not randomized in either of the studies.

If the subject meets the definition of a screen failure in this trial, 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

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary endpoints of the trial irrespective of whether or not the subject was administered all SC doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. For purposes of this trial, subjects who complete assessments at V5/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 V5/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 at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. 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 V5/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.

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	Any drug in this class	Should not be used as preventive therapy for migraine
NSAID	Any 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 irrespective of restriction conditions if given as a topical preparation or eye drops.

4.1.2 Restricted Concomitant Medications (Preventive Migraine Medications)

A small subgroup of subjects (up to 30%) will be allowed to use no more than 1 concomitant preventive migraine medication (see Table 4.1.2-1) at a stable dose and regimen during the trial if the medication was 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.

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[a]
Beta-blockers	Atenolol, propranolol, metoprolol, nadolol, and timolol
Calcium channel blocker/benzocycloheptene	Lomerizine, (flunarizine), and (pizotifen)
Antidepressants	Amitriptyline, venlafaxine, nortriptyline, and duloxetine
Antiepileptic medications	Topiramate, valproate, and (divalproate)

[a]Drugs that have not been approved in Japan are shown in parentheses.

Any of the medications listed above are allowed irrespective of restriction conditions if given as a topical preparation or as 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 when a subject signs the ICF to the end of trial date for individual subject.

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. Special attention should be paid to recording hospitalization or concomitant medications.

5.3 Immediately Reportable Events

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 $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ 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[23] (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 pregnancy test 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

The investigator is encouraged to contact the sponsor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor (ie, the investigator will be able to obtain the code break information independent of the sponsor). The investigator must contact the sponsor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the Clinical Safety and Pharmacovigilance department must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

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 ICF 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 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 scheduled 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. 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). 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.

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) or the time of withdrawal.

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. 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

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.

6.1.2 Pharmacokinetic Analysis

(1) Endpoint
Plasma TEV-48125 concentration

(2) Dataset for Analysis
Pharmacokinetic analysis set

(3) Analysis Method

1) Acceptance or nonacceptance of data will be determined in accordance with Section3.4, Exclusion from Pharmacokinetic Analysis, of the Manual Standard Practice for Noncompartmental Pharmacokinetic Analysis (Version 1.0).[24]
2) Concerning Section 6.1.2 (1), Endpoint, descriptive statistics will be calculated by treatment group for each blood sampling time point. 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 Population Pharmacokinetic Analysis

Using plasma concentration data, population pharmacokinetic analysis will be performed. A report will be separately prepared on the results of this analysis.

6.3 Immunogenicity

6.3.1 Immunogenicity Analysis Set

The immunogenicity analysis set will include all subjects in whom at least 1 dose of IMP is administered, and serum ADA is measured for at least 1 time point after IMP dosing.

6.3.2 Immunogenicity Analysis

Summary of immunogenicity results in the immunogenicity analysis set will be provided, and the incidence of immunogenicity expression will be calculated.

6.4 Pharmacogenomics

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

6.5 Biomarkers

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

7 Statistical Analysis

This section describes the statistical analysis scheduled to be performed as part of this trial. Further details of statistical analysis will be presented in the Statistical Analysis Plan that is separately prepared and will be finalized before unblinding.

7.1 Sample Size

In a phase 2b trial in CM patients (Trial LBR-101-021), concerning the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP, the difference between the TEV-48125 675/225/225 mg group and the placebo group was 1.7 days and the standard deviation was 4.9 days. On the assumption that this trial will also yield a similar result to the phase 2b trial (Trial LBR-101-021), a sample size of 176 subjects per group gives more than 90% power for the trial to succeed at a significance level of 0.05 (two-sided). Based on the above and taking into account a small percentage of subjects who may be excluded from the FAS, the target sample size was determined to be 180 subjects per group and 540 subjects as the overall total included in the trial.

7.2 Analysis Sets

- Enrolled set (ES):
  Subjects from whom informed consent has been obtained
- Randomized set (RS):
  Randomized subjects in the ES
- Safety set (SS):
  Subjects in the RS who receive the IMP at least once
- Full Analysis set (FAS):
  Subjects in the SS who have baseline and Week 12 data on monthly average number of headache days of at least moderate severity

7.3 Handling of Missing Data

The primary analysis of the primary endpoint will be performed using electronic headache diary data entered by subjects. No imputation will be performed for missing diary data.

7.4 Primary and Secondary Endpoint Analyses

7.4.1 Primary Endpoint Analysis

The primary endpoint is the mean change from baseline in the monthly (28 days) average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP.

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

Multiplicity problems will be avoided using a closed testing procedure. If superiority of the TEV-48125 675/225/225 mg group to the placebo group is confirmed at a two-sided significance level of 0.05, then the TEV-48125 675 mg/placebo/placebo group vs the placebo group will be tested at a two-sided significance level of 0.05.

7.4.2 Secondary Endpoint Analysis

The secondary efficacy endpoints in this trial are as follows:

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

2) Proportion of subjects reaching at least 50% reduction in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP
3) Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
4) Mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP in subjects not receiving concomitant preventive migraine medications
5) Mean change from baseline in disability score, as measured by the HIT-6, at 4 weeks after the final (third) dose of IMP

The secondary endpoints will be analyzed in the FAS. The same analysis used for the primary efficacy endpoint will be performed for the above endpoints, 1), 3), 4), and 5), using an ANCOVA model. For the endpoint 2), each TEV-48125 group and the placebo group will be compared using the Cochran-Mantel-Haenszel test stratified by baseline preventive medication use.

7.4.3 Exploratory Efficacy Endpoint Analysis

The exploratory 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 headache hours
- Number of days with use of any acute headache medications
- Number of days with nausea or vomiting
- Number of days with photophobia or phonophobia
- MSQOL
- EQ 5D-5L
- PHQ-2 and PHQ-9
- WPAI
- PGIC

The same analysis used for the primary or secondary endpoints will be performed as needed for the exploratory endpoints, using the FAS as the analysis set.

7.5 Analysis of Demographic and Baseline Characteristics

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

7.6 Safety Analysis

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

7.6.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized 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.

7.6.2 Clinical Laboratory Data

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

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

7.6.3 Vital Signs and Weight Data

For each treatment group, descriptive statistics will be calculated for vital sign and weight measurements and changes from baseline at each time point (including the final evaluation). 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.

7.6.4 Electrocardiogram Data

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

7.6.5 Injection Site Reactions

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

7.6.6 Electronic Columbia-Suicide Severity Rating Scale

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

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) or placebo.

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 (including investigational product or placebo) 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_406-102-00001_00002@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 specified 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 1), 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 CRF.

(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 (ie, at least 5 half-lives have passed since last use) or using no more than 1 preventive migraine medication 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.	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 1 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.
Protocol Synopsis Inclusion/Exclusion Criteria: 3.4.3; Table 3.4.3-1 Exclusion Criteria, No. 3	Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after use for at least 3 months at accepted migraine therapeutic doses: • Cluster A: divalproex sodium and sodium valproate • Cluster B: flunarizine and pizotifen	Patients who have previously failed (lack of efficacy) 2 or more of the clusters of the following medications for treatment of EM or CM after use for at least 3 months at accepted migraine therapeutic doses: • Cluster A: topiramate, divalproex sodium and sodium valproate • Cluster B: lomerizine, flunarizine

Protocol Section	Before Revision	After Revision
	• Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine • Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol	and pizotifen • Cluster C: amitriptyline, nortriptyline, venlafaxine, and duloxetine • Cluster D: atenolol, nadolol, metoprolol, propranolol, and timolol
3.7; Table 3.7-1 Schedule of Assessments	(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.
3.7; Table 3.7-1 Schedule of Assessments (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: −3 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	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

Protocol Section	Before Revision	After Revision
	case report form (CRF). • Visit date • Informed consent – Date of informed consent – Subject identification number • Result of eligibility assessment • Demographics – Date of investigation – Birth date, age, and sex – Childbearing potential (Reason for nonchildbearing potential, or contraceptive methods) – Race, ethnicity, and country – Medical history and complications	contraceptive methods) – Race, ethnicity, and country – Medical history and complications (at the time of informed consent)
4 Restrictions	Use of the following medications and concomitant therapies will be prohibited or restricted from after informed consent to V5/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 V5/End of treatment or the time of withdrawal.
4.1.2 Restricted Concomitant Medications (Preventive Migraine Medications)	A small subgroup of subjects (up to 30%) will be allowed to use no more than 1 concomitant preventive migraine medication (see Table 4.1.2-1) during the trial if the medication was 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.	A small subgroup of subjects (up to 30%) will be allowed to use no more than 1 concomitant preventive migraine medication (see Table 4.1.2-1) at a stable dose and regimen during the trial if the medication was 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.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

Amendment Number: 2

Issue Date: 18 Jun 2018

PURPOSE:

To clarify the text, correct errors, resolve inconsistencies throughout the text, reflect changes in the statistical analysis plan, etc.

BACKGROUND:

Revisions were made because unclear text, errors, etc, were found. Furthermore, on the basis of results from 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, Trial Duration	Overall trial period: Aug 2017 through Apr 2019 (planned)	Overall trial period: Aug 2017 through Sep 2019 (planned)
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.)
2.1 Trial Rationale	It is considered necessary to ..... and to demonstrate that the efficacy and safety of TEV-48125 in Japanese patients is similar to the efficacy and safety observed in the multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050), which warrants the implementation of this clinical trial.	It is considered necessary* to ..... and to demonstrate that the efficacy and safety of TEV-48125 in Japanese patients is similar to the efficacy and safety observed in the multinational phase 3 confirmatory trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050), which warrants the implementation of this clinical trial. (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation)
2.1 Trial Rationale	Prior to the implementation of this trial, ...	*Prior to the implementation of this trial, ... (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, ...	Both TEV-48125 dose groups showed improvement compared to the placebo group from Month 1, ...

Protocol Section	Before Revision	After Revision
3.1 Type/Design of Trial	For subjects who are lost to follow up, the end of trial date for individual subject is defined as the date of their last visit/contact or the date of the last attempt to contact them. Following ... for the purpose of evaluating ADA at 225 days (approximate equivalent of 5 half-lives) after the final dose of IMP (V4/Month 2) in this trial.	For *subjects who are lost to follow up*, the end of trial date for individual subject is defined as the date of their last visit/contact or the date of the last attempt to contact them. *Following ... for the purpose of evaluating ADA at 225 days (approximate equivalent of 5 half-lives) after the final dose of IMP (V4/Month 2) in this trial. (Note*: Minor revisions were made in the Japanese original, but no changes are required in the English translation.)
3.4.3 Exclusion Criteria	Screen failure subjects who fall under any of the exclusion criteria 1 to 5, 12, 19, and 20 during the screening period (including V1/Screening) may be rescreened only once if the characteristics of the exclusion criteria 1 to 5, 12, 19, and 20 have changed. 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.	Screen failure subjects may be rescreened if prior agreement is obtained from the sponsor. If a subject is to be rescreened, informed consent must be newly obtained, and a new subject identification number must be assigned to the subject prior to performing the rescreening examination.
Protocol Synopsis, Criteria for Evaluation; 3.5.2.1 Efficacy Endpoints	• Mean change from baseline in the monthly average number of days of use of any acute migraine medications during the 12-week period after the first dose of IMP	• Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
Protocol Synopsis, Criteria for Evaluation; 3.5.2.1 Efficacy Endpoints	• Mean change from baseline in the number of migraine days during the 4-week period after the first dose of IMP	(Deleted)
3.5.3 Exploratory Endpoints	• Number of days of use of any acute headache medications • Number of subjects discontinuing concomitant preventive migraine medications during the treatment period	• Number of days with use of any acute headache medications • (Deleted)
3.5.5 Immunogenicity Endpoints	• Impact of serum anti-TEV-48125 antibodies on pharmacokinetics, efficacy, and safety	(Deleted)

Protocol Section	Before Revision	After Revision
3.6 Measures to Minimize/Avoid Bias	In the event that a medical emergency occurs to a subject and knowledge of the IMP assignment code is considered essential to adequately treat the subject, ...	In the event that a subject experiences a medical emergency or the safety of a subject needs to be confirmed immediately and knowledge of the IMP assignment code is considered essential to adequately treat the subject, ...
3.7 Trial Procedure, Table 3.7-1	[d]Procedure will be performed before other assessments (eg., blood draws and administration of questionnaires).	[d]Procedure will be performed before other assessments (blood draws and administration of questionnaires).
3.7.1.1.1 Visit 1/Screening (Day −28; Acceptable Window: −3 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)	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.	(Deleted)
3.7.1.2.1.1 Visit 2/Baseline (Day 1); 3.7.1.2.3 Visit 5/End of Treatment (Day 85; Acceptable Window: ±3 Days) and Withdrawal (Acceptable Window: Day of Withdrawal Decision + 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)
3.7.1.2.2 Visit 3/Month 1 (Day 29; Acceptable Window: ±3 Days) and Visit 4/Month 2 (Day 57; Acceptable Window: ±3 Days)	• 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)
3.7.1.3 Two Additional Visits for Pharmacokinetic Analysis (3 to 10 Days and 14 to 21	• Triplicate 12-lead ECGs (should precede other scheduled assessments including blood sampling and questionnaires)	• Triplicate 12-lead ECGs (should precede blood sampling)

Protocol Section	Before Revision	After Revision
Days After One of the IMP Administrations at Either Visit 2/Baseline, Visit 3/Month 1, or Visit 4/Month 2)		
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). 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. 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 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). 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. 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	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). The same position and arm should be used each time vital signs are measured for a given subject.	As vital signs, systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate will be measured before other assessments (blood draws and questionnaires). 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 the occurrence of an AE, the 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	Subjects will be allowed to use acute migraine medication to treat acute	Subjects will be allowed to use acute headache medication only at the time of

Protocol Section	Before Revision	After Revision
Medications	migraine attacks, as needed, but will not be allowed to use it as preventive medication.	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	Angiotensin receptor blockers	Angiotensin receptor blockers/ angiotensin converting enzyme inhibitors
4.2 Prohibited Concomitant Therapies	Use of an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for treating CM will be prohibited.	Use of an intervention/device (eg, scheduled nerve blocks and transcranial magnetic stimulation) for treating migraine will be prohibited.
5.1 Definitions	• ...or the development of drug dependency or drug abuse. – Any potential	• ...or the development of drug dependency or drug abuse. Any potential ... .
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.	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.
6.3.2 Immunogenicity Analysis	The impact of immunogenicity on the pharmacokinetics, efficacy, and safety will be evaluated.	(Deleted)
7.4.2 Secondary Endpoint Analysis	3) Mean change from baseline in the monthly average number of days of use of any acute migraine medications during the 12-week period after the first dose of IMP	3) Mean change from baseline in the monthly average number of days with use of any acute headache medications during the 12-week period after the first dose of IMP
7.4.2 Secondary Endpoint Analysis	4) Mean change from baseline in the number of migraine days during the 4-week period after the first dose of IMP	(Deleted) The numbers that followed 4) were shifted up to replace 4) onward.
7.4.2 Secondary Endpoint Analysis	The same analysis used for the primary efficacy endpoint will be performed for the above endpoints, 1), 3), 4), 5), and 6), using an ANCOVA model.	The same analysis used for the primary efficacy endpoint will be performed for the above endpoints, 1), 3), 4), and 5), using an ANCOVA model.
7.4.3 Exploratory Efficacy Endpoint Analysis	• Number of days of use of acute headache medications • Number of subjects discontinuing concomitant preventive migraine medications during the treatment period	• Number of days of use of any acute headache medications • (Deleted)
7.6.4 Electrocardiogram Data	For the results of assessments (normal or abnormal), a shift table from baseline will be displayed.	For the results of assessments, a shift table from baseline will be displayed.

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 Sep 2019 (planned)	Overall trial period: Aug 2017 through Jan 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 clarify 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.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
Protocol Synopsis, Trial Duration	Overall trial period: Aug 2017 through Jan 2020 (planned)	Overall trial period: Aug 2017 through Mar 2020 (planned)
3.7.2.5. EuroQol-5 Dimension, 5 Response Level Version Questionnaire	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.	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. (Note*: A minor revision was made in the Japanese original, but no changes are required in the English translation.)
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.
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. 19	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.