CLINICAL STUDY PROTOCOL

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

NCT Number: NCT04355117
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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
TEV-48125 (generic name: fremanezumab)

CLINICAL PROTOCOL

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

A safety evaluation trial of TEV-48125 self-administered in migraine patients

Protocol No. 406-102-00005

CONFIDENTIAL — PROPRIETARY INFORMATION

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1 Protocol Summary

1.1 Synopsis

Name

Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product:

TEV-48125

Protocol No.:

406-102-00005

Protocol Title:

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

Protocol Lay Person Short Title:

A safety evaluation trial of TEV-48125 self-administered in migraine patients

Clinical Phase/Trial Type:

Phase 3/Dose-tolerance trial

Treatment/Indication:

Migraine

Objectives and Endpoints:

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

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

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

Trial Design:

This trial is a multicenter, open-label trial in migraine patients and will consist of a 4-week screening period and an 8-week treatment period.

Trial Population:

A total of 50 migraine patients age 18 to 70 years, inclusive, with a history of migraine (according to International Classification of Headache Disorders [ICHD-3] criteria*), or who have been clinically diagnosed with migraine and whose medical history is not better accounted for by another ICHD-3 diagnosis for ≥ 12 months prior to giving informed consent

*The International Classification of Headache Disorders, third edition (ICHD-3), Headache Classification Committee of the International Headache Society, 2018

Key Inclusion/Exclusion Criteria:

Key Inclusion Criteria:

1) Patient has a history of migraine (according to the ICHD-3 criteria) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to giving informed consent.
2) Patient fulfills any of the following criteria on ≥ 4 days in baseline information collected during the 28-day screening period.
   - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura
   - ICHD-3 diagnostic criteria B and C for 1.2 Migraine with aura
   - Probable migraine (a migraine subtype where only 1 migraine criterion is missing)
   - The patient used a triptan or ergot derivative to treat an established headache.
3) Not using preventive migraine medications for migraine or other medical conditions (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medications (restricted medications, see Table 6.5.2-1) 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 screening examination (Visit 1/Screening).
4) Patient demonstrates compliance with the electronic headache diary (eDiary) 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.

5) At the time of informed consent, patient whom the investigator judges fit for self-administration of the IMP

Key Exclusion Criteria:

1) Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator
2) History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
3) Prior exposure to a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) pathway meeting the following conditions:
   - Less than 5 months has passed since the final administration of AMG334, LY2951742, or ALD304.
   - Less than 1 year has passed since the final administration of TEV-48125 (prefilled syringe). (Even if 1 year has passed since the final administration, patient cannot be enrolled if assessment of anti-drug [TEV-48125] antibody [ADA] due to the previous administration is positive or inconclusive.)
4) The patient cannot participate or successfully complete the trial for other reasons in the opinion of the investigator.

Trial Site(s):

Approximately 10 trial sites are planned in Japan.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

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

The IMP is to be removed from the refrigerator and left to stand at room temperature for 30 minutes before administration.

Trial Assessments:

Assessments for safety: adverse event, clinical laboratory tests, 12-lead electrocardiogram (ECG), physical examination findings, vital signs, weight, injection site reaction (erythema, induration, ecchymosis, and/or pain), Columbia-Suicide Severity Rating Scale (C-SSRS), prior medication, concomitant medication, prior and concomitant therapy, and plasma drug concentration

Screening/Other: Subject demographics, eDiary data (headache data), and serum ADA assessment

Data Monitoring Committee: None

Statistical Methods:

- Safety analysis

The incidence of treatment-emergent AEs (TEAEs) will be summarized. Other safety endpoints will be summarized using descriptive statistics, shift tables, or frequency distributions.

- Sample size

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

Trial Duration:

- Expected duration of trial participation for each individual subject: 85 days
- Screening period: 4 weeks (28 days)
- Treatment period: 8 weeks (57 days)

The expected overall trial duration from the time informed consent is obtained from the first subject to completion of final examination of the last subject is 7 months.

1.2 Schema

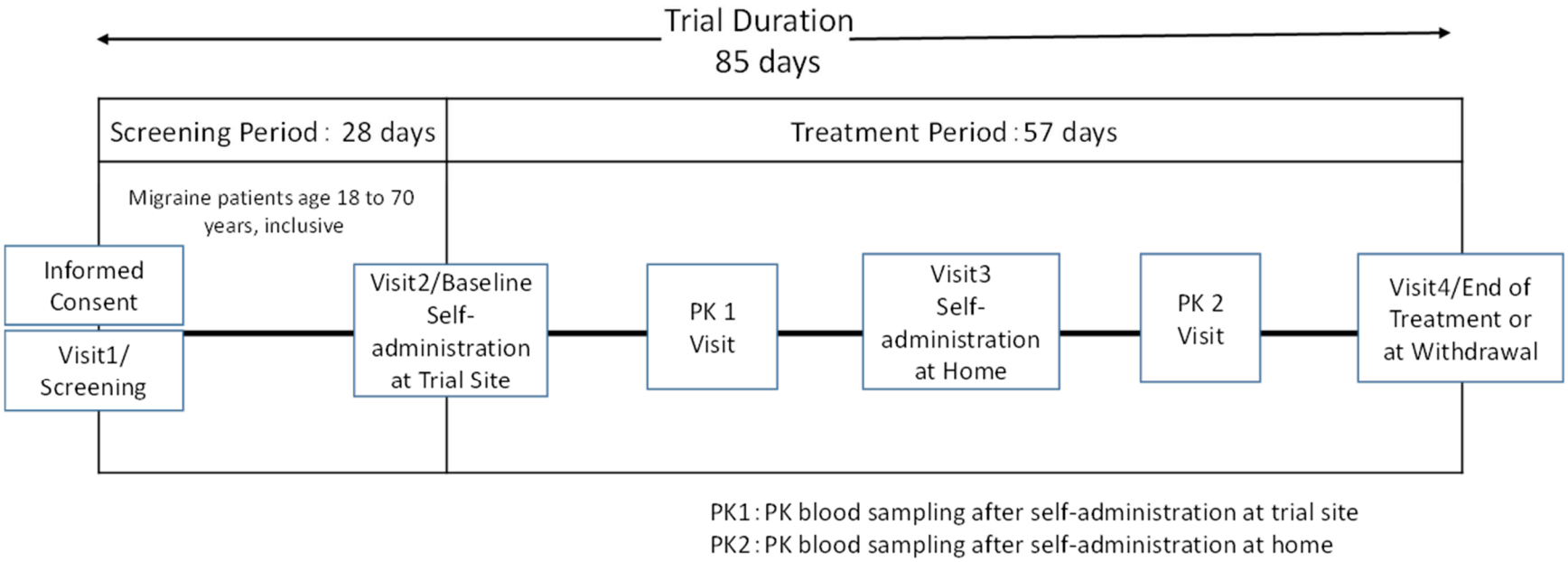

Figure 1.2-1 Trial Design Schematic

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Item	Period	Screening Period	Treatment Period					
	Visit	V1/ Screening	V2/Baseline Self-administration at Trial Site	PK1 Visit (PK Blood Sampling After Administration at Trial Site)	V3[a] Self-administration at Home	PK2 Visit (PK Blood Sampling After Administration at Home)	V4/End of Treatment	At Withdrawal
	Trial Day[b]	Day −28	Day 1	Day 4 to Day 11	Day 29	Day 32 to Day 39	Day 57	
	Acceptable Window	−3			±3		±3	Day of Withdrawal Decision + 7[c]
Informed Consent[d]		X						
Enrollment[e]			X					
Demographics		X						
Inclusion/Exclusion Criteria		X	X					
Instruction on IMP Handling and Self-administration Procedure		X	X		X			
Assessment/Confirmation That Self-administration Is Possible			X		X			
IMP Self-administration[f]			X		X[a]			
Confirmation of Self-administration Execution Status[f]			X		X	X		
Confirmation of Compliance With Self-administration Procedure[f]			X		X	X		
Injection Site Reaction Assessment[g]			X			X		
Physical Examination		X	X		X		X	X
Height		X						
Weight		X	X		X		X	X
12-Lead ECG		X	X		X		X	X
Vital Signs (systolic and diastolic pressure, pulse rate, temperature, respiratory rate)		X	X		X		X	X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)		X	X		X		X	X
Urine hCG Test[h]		X	X		X		X	X

Table 1.3-1 Schedule of Assessments

Item	Period	Screening Period	Treatment Period					
	Visit	V1/ Screening	V2/Baseline Self-administration at Trial Site	PK1 Visit (PK Blood Sampling After Administration at Trial Site)	V3[a] Self-administration at Home	PK2 Visit (PK Blood Sampling After Administration at Home)	V4/End of Treatment	At Withdrawal
	Trial Day[b]	Day −28	Day 1	Day 4 to Day 11	Day 29	Day 32 to Day 39	Day 57	
	Acceptable Window	−3			±3		±3	Day of Withdrawal Decision + 7[c]
Adverse Events[i]	←	———	———	———	———	———	———	→
Medication and Therapy Inquiry	←	———	———	———	———	———	———	→
AI Device Deficiency[j]		X		X	X			
C-SSRS[k]		X		X		X	X	
Blood Sampling for Plasma Drug Concentration[l]			X	X	X	X	X	
Blood Sampling for Serum ADA Assessment[m]		X		X		X	X	
eDiary Device Provided and Explained[n]	X							
Data Entry in eDiary[o]	←	———	———	———	———	———	———	→
Review of eDiary		X		X		X	X	
Return of eDiary Device						X	X	

hCG = human chorionic gonadotropin; IMP = combination product of TEV-48125 and AI; PK = pharmacokinetic; V = visit.

[a]After completion of the specified items and reconfirmation that self-administration at home is possible at Visit 3, the subject will perform self-administration at home. Visit 3 and the day of self-administration at home do not have to be the same day, but self-administration at home must be performed within 3 days from the day of Visit 3 (including the day of Visit 3) and also must be performed within the acceptable window for Visit 3.

[b]Trial Day is indicated on the basis of Visit 2/Baseline being Day 1 and self-administration at home being performed on Day 29.

[c]Withdrawal examination will not be performed for subjects withdrawn prior to self-administration at the trial site. For subjects withdrawn after self-administration, withdrawal examination is to be performed within 7 days from the day of the withdrawal decision.

[d]Informed consent can be obtained prior to the day of Visit 1/Screening.

[e]The investigator will confirm that each subject meets all of the inclusion criteria and does not fall under any of the exclusion criteria and enroll subjects who are judged to be eligible.

[f]Following self-administration, the execution status of self-administration and compliance with the self-administration procedure will be recorded. For self-administration at the trial site, the investigator will record the information after completion of self-administration. For self-administration at home, the subject will record the information using a check sheet and when the subject visits the trial site the

investigator will perform a confirmation based on an interview and the information recorded by the subject.

[g]Assessment of injection site reaction will be performed immediately after administration and at 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 and/or pain is of moderate or less severity. The investigator will perform the assessment after completion of self-administration at the trial site. For self-administration at home (Visit 3/Self-administration at Home), the subject will assess and record injection site reaction and at PK blood sampling visit 2 at 3 to 10 days after self-administration at home the investigator will perform a confirmation based on an interview and the information recorded by the subject.

[h]Women of childbearing potential only. If the result of urine hCG test at screening is positive, serum hCG will be tested to confirm that the result is negative. If the result of urine hCG test is positive at Visit 2 or Visit 3, the subject is to be withdrawn from the trial.

[i]Inquiries about AEs will be made before and after IMP administration. Postdose inquiries following self-administration at the trial site will be made before the subject leaves the trial site. For self-administration at home, when the subject visits the trial site the investigator will perform assessment based on an interview and the information recorded by the subject.

[j]Deficiencies with the AI device occurring from the time the IMP is provided to the subject to the completion of self-administration are to be recorded in the electronic case report form (eCRF).

[k]The C-SSRS Baseline Version will be completed at Visit 2/Baseline, and the C-SSRS Since Last Visit Version will be completed at all subsequent visits.

[l]Blood sampling for plasma drug concentration determination at Visit 3 will be performed before administration. The following blood sampling timepoints are also set:

Visit 2 (self-administration at trial site):

One timepoint between 3 to 10 days postdose (PK1 visit) and one timepoint at 28 days (± 3 days) postdose (Visit 3), for a total of 2 timepoints

Visit 3 (self-administration at home):

One timepoint between 3 to 10 days postdose* (PK2 visit) and one timepoint at 28 days (± 3 days)** postdose (Visit 4/End of Treatment), for a total of 2 timepoints

*Taking into consideration the acceptable window and using the day of self-administration at home at Visit 3 as the starting point, blood sampling will be performed between Day 29 and Day 42.

**Taking into consideration the acceptable window and using the day of self-administration at home at Visit 3 as the starting point, blood sampling will be performed between Day 51 and Day 63.

[m]Blood sampling for serum ADA assessment at Visit 2/Baseline will be performed before administration. Blood sampling for ADA assessment will also be performed if severe hypersensitivity reaction (eg, anaphylaxis) is suspected.

[n]Subjects who meet the inclusion criteria will be provided with the eDiary device at Visit 1/Screening, instructed on how to use it, and given an explanation of the compliance requirements.

[o]Subjects are to enter headache data in the eDiary every day from Visit 1/Screening until the day before Visit 4/End of Treatment or withdrawal.

1.3.1 Screening Period

1.3.1.1 Date of Informed Consent

The screening period is from the day of informed consent until trial enrollment.

The investigator will obtain an appropriately signed and dated informed consent form before commencing any screening procedures. The following information will be recorded in the electronic case report form (eCRF):

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

1.3.1.2 Visit 1/Screening

The start of Visit 1/Screening is 28 days before Visit 2/Baseline. In order to confirm that the subject meets all of the inclusion criteria and does not fall under any of the exclusion criteria, the following assessments, tests, and observations are to be performed and the information recorded in the eCRF.

- Visit date
- Result of eligibility assessment
- Demographics
  - Date of investigation
  - Birthdate, age (at the time of informed consent), and sex
  - 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 medications and therapies (within 5 months before the start of IMP administration)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- 12-Lead ECG
- Physical examination
- Height and weight (Body mass index [BMI] will be calculated using height and weight at Visit 1/Screening.)
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine human chorionic gonadotropin (hCG) test (women of childbearing potential [WOCBP] only) (If the result of urine hCG test is positive at screening, serum hCG test will be performed to confirm that the result is negative.)
- eDiary (Subjects will be provided with the eDiary device, instructed on how to use it, and given an explanation of the compliance requirements.)

- AEs
- Instruction on IMP* handling and the self-administration procedure

*The IMP is a combination product of TEV-48125 and the AI.

Twelve-lead ECG and clinical laboratory test results measured by the central laboratory, which cannot be assessed at the start of Visit 1/Screening, should be checked against the inclusion and exclusion criteria as soon as they become available to confirm the subject's eligibility.

For headache data on each day from Visit 1/Screening through the day before Visit 2/Baseline, subjects are to enter headache information for the previous day in the eDiary. The eDiary data of the most recent 28 days prior to Visit 2/Baseline will be used to determine whether inclusion criteria 5 is met.

1.3.2 Treatment Period

1.3.2.1 Visit 2/Baseline (Day 1): Self-administration at the Trial Site

The treatment period is from the time of trial enrollment until Visit 4/End of treatment or the time of withdrawal. On each day during the treatment period, subjects are to enter headache data for the previous day in the eDiary.

The investigator will confirm that each subject meets all of the inclusion criteria and does not fall under any of the exclusion criteria, and enroll subjects who are judged to be eligible. Subjects who are judged to be ineligible will be handled as screen failures.

For subjects who are judged to be eligible, prior to IMP administration the following assessments, tests, and observations are to be performed and the information recorded in the eCRF.

- Visit date
- Result of eligibility assessment
- Use of preventive migraine medications
- eDiary
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- 12-Lead ECG
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine hCG test (WOCBP only)

- Blood sampling for serum ADA assessment
- C-SSRS (Baseline Version)
- History of medications and therapies (within 5 months before the start of IMP administration)
- AEs
- Instruction on IMP handling and the self-administration procedure
- Judgment on whether self-administration at the trial site is possible

After the above predose assessments, tests, and observations are completed, subjects whom the investigator judges fit for self-administration will perform self-administration at the trial site under the supervision of the investigator (see Section 6.1). After self-administration by the subject, the investigator will perform the following assessments and observations and record the information in the eCRF. Additional assessments may be performed based on the severity of abnormal injection site reaction (erythema, induration, ecchymosis, and/or pain).

- Execution status of self-administration
  - Date, time, injection site, confirmation of the amount of drug solution remaining in the AI, and leakage of drug solution on the skin after subcutaneous injection
- Occurrence of injection site reaction (erythema, induration, ecchymosis, and/or pain) and its severity (immediately after administration and at 1 hour postdose)
- Compliance with self-administration procedure
- Judgment on whether self-administration at home is possible
- Deficiency with the AI device
- AEs

The investigator will assess the subject's compliance with the procedure for self-administration at the trial site. If it is judged that self-administration by the subject at home is not possible, the subject will be withdrawn from the trial.

1.3.2.2 Pharmacokinetic Blood Sampling Visit 1 (PK1 Visit)

At 3 to 10 days after IMP administration at Visit 2/Baseline, the following assessments, tests, and observations will be performed and the information recorded in the eCRF.

- Visit date
- Blood sampling for plasma drug concentration measurement
- AEs

1.3.2.3 Visit 3: Self-administration at Home

Prior to IMP administration, the following assessments, tests, and observations will be performed and the information recorded in the eCRF.

- Visit date
- eDiary
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- 12-Lead ECG
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine hCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood sampling for plasma drug concentration measurement
- C-SSRS (Since Last Visit Version)
- Concomitant medications and therapies
- AEs
- Instruction on IMP handling and the self-administration procedure
- Reconfirmation that self-administration at home is possible

After the above predose assessments, tests, and observations are completed, subjects who understand the instructions on IMP handling and the self-administration procedure and for whom it is reconfirmed that self-administration at home is possible will perform self-administration at home according to "Procedure for TEV-48125 AI Self-administration" (see Section 6.1). Self-administration at home must be performed within 3 days from the day of Visit 3 (including the day of Visit 3) and must also be performed within the acceptable window for Visit 3 (± 3 days: Day 26 to Day 32).

The investigator will contact the subject via telephone or other means on the day of self-administration at home, or as soon as possible thereafter if contact on the day of self-administration is not possible, and confirm whether self-administration was performed. If occurrence of an AE or any incidence is reported, the subject will be requested to promptly visit the trial site as needed.

1.3.2.4 Pharmacokinetic Blood Sampling Visit 2 (PK2 Visit)

At 3 to 10 days after IMP administration at Visit 3 (self-administration at home), the investigator will confirm the execution status of self-administration at home and

compliance with the self-administration procedure recorded by the subject, perform the following assessments, and record the information in the eCRF (to be performed by Visit 4/End of Treatment at the latest).

- Visit date
- Execution status of self-administration at home
  - Date, time, injection site, confirmation of amount of drug solution remaining in the AI, and leakage of drug solution on the skin after subcutaneous injection
- Occurrence of injection site reaction (erythema, induration, ecchymosis, and/or pain) and its severity (immediately after administration and at 1 hour postdose)
- Compliance with self-administration procedure
- Deficiency with the AI device
- AEs
- Blood sampling for plasma drug concentration measurement

1.3.2.5 Visit 4/End of Treatment or at Withdrawal

As the final evaluation (Visit 4/End of Treatment), the following assessments, tests, and observations will be performed. For withdrawals, the following assessments, tests, and observations will be performed wherever possible within the acceptable window. The results of the assessments, tests, and observations will be recorded in the eCRF.

- Visit date
- Completion of trial
  - Trial completion date or withdrawal date
  - In the case of withdrawal, reason for withdrawal
- eDiary (Subject is to return the eDiary device.)
- Vital signs (systolic and diastolic blood pressure, pulse rate, temperature, and respiratory rate)
- 12-Lead ECG
- Physical examination
- Weight
- Clinical laboratory tests
  - Chemistry, hematology, coagulation, and urinalysis
  - Urine hCG test (WOCBP only)
- Blood sampling for serum ADA assessment
- Blood sampling for plasma drug concentration measurement
- C-SSRS (Since Last Visit Version)

- Concomitant medications and therapies
- AEs

1.3.3 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, and observations will be performed. The date of the unscheduled visit and the results of the assessments, tests, and observations (only those performed according to the procedures specified in the protocol) will be recorded in the eCRF. Other procedures may be performed at the discretion of the investigator.

2 Introduction

TEV-48125 (generic name: fremanezumab) is a monoclonal antibody that potently and selectively binds to calcitonin gene-related peptide (CGRP). By blocking the binding activity of the CGRP receptor,[1,2] TEV-48125 is expected to be effective in preventing migraine attacks and is currently undergoing clinical development.

Refer to the fremanezumab (TEV-48125) Investigator's Brochure (IB) for more detailed information.

2.1 Trial Rationale

In foreign countries, based primarily on the results of 2 double-blind, placebo-controlled trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050) and a long-term trial (Trial TV48125-CNS-30051) in chronic and episodic migraine (CM and EM) conducted as multinational phase 3 trials evaluating the efficacy and safety of subcutaneous administration of TEV-48125 for the preventive treatment of migraine, use of TEV-48125 as a prefilled syringe (PFS) preparation capable of being self-administered was approved for the preventive treatment of migraine in the US in September 2018 and in the EU in March 2019. Regarding self-administration, in a foreign human factor validation study of a TEV-48125 autoinjector (AI) preparation, most of the participating healthcare professionals, patients, and caregivers were able to use the AI appropriately according to the instructions, and in a post-study survey more than 80% of the participants reported that the AI was easy to use and that they could use it with confidence.[3] Bioequivalence between the TEV-48125 AI preparation and the PFS preparation was then demonstrated in a bioequivalence study (TV48125-BE-10145), and registration applications for the AI preparation capable of self-administration as an additional fremanezumab preparation were filed in the US in March 2019 and in the EU

in May 2019. Those applications are currently under review in both regions as of September 2019.

In Japan, as of September 2019, as phase 2b/3 trials evaluating the efficacy and safety of subcutaneous administration of TEV-48125 for the preventive treatment of migraine, 2 double-blind, placebo-controlled trials (Trials 406-102-00001 and 406-102-00002) and a long-term trial (Trial 406-102-00003) are being conducted using the PFS preparation (not intended for self-administration). Although Otsuka's initial submission for approval of TEV-48125 is planned only for the PFS preparation (not intended for self-administration), as there is a strong medical need for treatment by self-administration at home, an additional application for an AI preparation capable of self-administration (at home) is also being planned with the aim of increasing patient convenience.

The AI device to be used in the present trial is pre-filled with a single dose of 225 mg. The drug is administered by removing the protective cap and pressing the AI against the skin at the injection site. The injection needle is concealed behind a shield, and when the AI is lifted away from the skin after injection the shield returns to its original position and the needle is again concealed, thus preventing accidental needle injury. This is the same mechanism as the device used in the foreign human factor validation study.

Based on the above, it is considered appropriate to conduct the present trial to assess the safety of TEV-48125 when subcutaneously self-administered at home using an AI in Japanese migraine patients.

2.2 Background

Migraine is a recurrent headache disorder manifesting in attacks lasting 4 to 72 hours. The headaches are unilateral and/or pulsating and of moderate or severe intensity and aggravated by routine physical activity. Migraine attacks associated with nausea and/or photophobia and phonophobia[4] are reported to impose a considerable burden on the daily and social lives of affected individuals.[5,6,7] Migraine affects more than 10% of adults worldwide[8] and in a 1997 nationwide survey of the population aged 15 years or older, the prevalence of migraine in Japan was reported to be 8.4%, with a female/male ratio of 3.6. The highest prevalence (approximately 20%) was in women age 30 to 39.[9] In a treatment status survey of physicians conducted in 2019 by INTAGE Healthcare Inc, the number of migraine patients under medication in Japan was estimated to be 666,000.[10]

The prevalence of migraine in Japanese age 20 to 59, the majority of the school or working age population, is approximately 3% to 7% for males and 11% to 20% for females, with the highest prevalence in the 20 to 39 age groups.[9] As the daily lives of

people in this age range are predominantly occupied by school, work, or housework, the need for long-term regular clinical visits for medication administration is a time and mental burden, and this burden may lead to decreased treatment adherence.[11,12,13] Decreased adherence is generally considered to be one cause of poor disease control, and in migraine patients, insufficient treatment efficacy increases the risk of progression from EM to CM.[14] This would suggest that there is strong medical need for treatment by self-administration of TEV-48125 at home. From the perspective of treatment continuation, it is considered meaningful to minimize the number of clinical visits and alleviate the impact on daily life by adding self-administration of TEV-48125 using an AI as a treatment option tailored to patients' lifestyles.

2.3 Known and Potential Risks and Benefits

Identified risks (adverse drug reactions) of TEV-48125 include injection site induration, injection site erythema, injection site pruritus, and injection site rash. Being a protein injection, there is a potential risk that TEV-48125 could cause severe hypersensitivity reactions such as type I hypersensitivity or allergic reaction and type III hypersensitivity reaction. Neither anaphylaxis nor severe hypersensitivity reactions to TEV-48125 were reported in placebo-controlled, double-blind, phase 2b trials evaluating the efficacy and safety of subcutaneous administration of TEV-48125 (Trials LBR-101-021 and LBR-101-022) and Trials TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 in CM and EM patients. Likewise, these events did not occur in healthy subjects. Among all subjects who participated in placebo-controlled trials, 2 placebo-treated subjects (< 1%) and 2 TEV-48125-treated subjects (< 1%) experienced drug hypersensitivity (moderate and mild in severity in 1 subject each). Aside from these events, among all TEV-48125-treated subjects, 3 subjects experienced an adverse event (AE) of drug hypersensitivity (moderate in 2 subjects and mild in 1 subject). All drug hypersensitivity events reported in this clinical development program were non-serious; they all resolved after corticosteroid and/or antihistamine therapies, with the outcome classified as recovery.

In efficacy evaluation in 2 completed phase 2b trials and 2 completed phase 3 trials conducted thus far, statistically significant and clinically meaningful improvement from baseline was demonstrated in TEV-48125-treated subjects vs placebo-treated subjects.

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

Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

3 Objectives and Endpoints

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

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

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

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
To assess the safety of TEV-48125 when subcutaneously self-administered in migraine patients at home	Primary Endpoint: • Safety (occurrence of AEs) Other Endpoints: • Execution status of self-administration at home • Subject compliance with the self-administration procedure • Deficiencies with the AI device Exploratory Endpoint: • Efficacy (number of migraine days, number of headache days, and number of headache days of at least moderate severity)

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This trial is a multicenter, open-label trial in migraine patients. The schematic of the trial design is shown in Figure 1.2-1 and trial assessment time points are summarized in Table 1.3-1.

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

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

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

The investigator will confirm whether the subject is able to perform self-administration in compliance with the procedure, and judge whether self-administration at home is possible. Subjects for whom the investigator judges self-administration at home to be possible will perform self-administration using the AI at home after performing protocol-specified procedures at Visit 3. Subjects will be asked to visit the trial site for blood sampling for plasma drug concentration measurement at 3 to 10 days after IMP administration at Visit 2/Baseline and Visit 3. At 4 weeks after final IMP administration (self-administration at home) subjects will visit the trial site for the final evaluation (Visit 4/End of Treatment). For subjects who are withdrawn from the trial, a withdrawal examination will be performed wherever possible.

4.2 Scientific Rationale for Trial Design

In order to apply for marketing approval of TEV-48125 in Japan as a drug that can be self-administered at home, it is necessary to demonstrate in a clinical trial that self-administration of TEV-48125 using an AI at home can be performed without any problem in clinical practice in Japan. In an attempt to demonstrate the safety of self-administration of TEV-48125 using an AI at home, the present trial will evaluate the safety of TEV-48125 based on the occurrence of AEs and comprehensively assess the

feasibility of self-administration of TEV-48125 using an AI at home by evaluating the execution status of self-administration at home and subject compliance with the self-administration procedure. The trial will also assess any deficiencies with the AI device.

Currently, clinical trials of the PFS preparation of TEV-48125 (not intended for self-administration) are ongoing in CM and EM patients. Once the trials demonstrate superiority of TEV-48125 to placebo, an application for marketing approval will be made for the indication of "preventive treatment of migraine" in patients with migraine (EM and CM). The planned target patients for self-administration of TEV-48125 using an AI are the same patients population enrolled in the trials using the PFS preparation. The present trial will therefore include male and female migraine patients (age 18 to 70 years, inclusive), who have a history of migraine (according to the International Classification of Headache Disorders, third edition [ICHD-3] criteria[a]) or for whom clinical assessment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to giving informed consent, and who meet the inclusion criteria based on the baseline information collected during the 28-day screening period. In addition, as this trial is designed to evaluate efficacy in an exploratory manner, eligible subjects must have migraine attacks on ≥ 4 days during the screening period.

Considering the use for self-administration at home, it is appropriate that the subject should perform self-administration only after the investigator has given adequate training to the subject and only if it has been confirmed that the subject is able to perform self-administration appropriately. In this trial, the investigator will first instruct the subject on the self-administration procedure, and then subjects will self-administer the initial dose of TEV-48125 using the AI under the supervision of the investigator at the trial site. Only subjects who are judged by the investigator to be able to perform self-administration at home according to the procedure will be allowed to subcutaneously self-administer the second dose of TEV-48125 using the AI at home.

In conclusion, the sponsor considered that this trial in Japanese migraine patients will be able to show the safety of self-administration using an AI at home.

4.3 Dosing Rationale

The dosing regimen in the trial is 225 mg of TEV-48125 administered once monthly (2 doses in total).

[a] Diagnosis in accordance with the International Classification of Headache Disorders, third edition (ICHD-3) diagnostic criteria (Headache Classification Committee of the International Headache Society 2018)

Each AI to be used in the trial contains 225 mg/1.5 mL (150 mg/mL) of TEV-48125. The dose of TEV-48125 in the trial is 225 mg, which is the dosing unit.

The safety of TEV-48125 administered at 225 mg once monthly (except for an initial dose of 675 mg in CM subjects) was demonstrated in multinational phase 3 trials (Trials TV48125-CNS-30049 and TV48125-CNS-30050) in CM and EM patients (including Japanese patients), the data from which were included in the dossier submitted upon application for marketing approval in the EU and US. Therefore, administering the dose of 225 mg once monthly for 2 months is considered appropriate.

4.4 End of Trial Definition

The end of trial date is defined as the last date of contact or examination or the date of final contact attempt as recorded on the electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

4.5 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or exploratory objectives of the trial irrespective of whether or not the subject actually subcutaneously self-administered all 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 assessment at Visit 4/End of treatment will be defined as trial completers.

5 Trial Population

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

Subjects who are using preventive migraine medications (see Table 6.5.2-1 List of Restricted Concomitant Medications (Preventive Migraine Medications)) will be permitted to continue using no more than 2 preventive migraine medications only if the dose and regimen have been stable for at least 2 months prior to screening examination (Visit 1/Screening).

5.1 Subject Selection and Numbering

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

site serial number) will be given at each trial site in the chronological order informed consent is obtained in, starting at 00001. Following screening, subjects who fail to meet the eligibility criteria will be handled as screen failures. Trial sites will prepare and retain a list of all consented subjects and their subject identification numbers.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted by the investigator during the trial.

5.2.1 Inclusion Criteria

Subjects are required to meet the following inclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Males or females age 18 to 70 years, inclusive, at the time of informed consent
2) Patient with migraine onset at ≤ 50 years of age
3) Patient signs the informed consent document before start of the trial
4) Patient has a history of migraine (according to the ICHD-3 criteria) or clinical judgment suggests a migraine diagnosis (not better accounted for by another ICHD-3 diagnosis) for ≥ 12 months prior to giving informed consent.
5) Patient fulfills any of the following criteria on ≥ 4 days in baseline information collected during the 28-day screening period.
   - ICHD-3 diagnostic criteria C and D for 1.1 Migraine without aura (see Section 10.4)
   - ICHD-3 diagnostic criteria B and C for 1.2 Migraine with aura (see Section 10.4)
   - 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 6.5.1-1, List of Prohibited Concomitant Medications (Preventive Migraine Medications), and Table 6.5.2-1, List of Restricted Concomitant Medications (Preventive Migraine Medications)) for migraine or other medical conditions (ie, at least 5 half-lives have passed since last use) or using no more than 2 preventive migraine medications (restricted medications, see Table 6.5.2-1, List of Restricted Concomitant Medications (Preventive Migraine Medications)) 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 screening examination (Visit 1/Screening).
7) Body mass index (BMI) between 17.5 to 37.5 kg/m^2 and a total weight between 35.0 and 120.0 kg, inclusive
8) Patient demonstrates compliance with the electronic headache diary (eDiary) 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) At the time of informed consent, patient whom the investigator judges fit for self-administration of the IMP
10) 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), 6), 8), and 10): These criteria were set to appropriately evaluate efficacy and safety.

2), 4), and 5): These criteria were set to identify patients with migraine.

3): This criterion was set to ensure conduct of the trial in an ethically appropriate manner.

7) and 9): These criteria were set to ensure appropriate and safe administration of the IMP.

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at the time points described in the schedule of assessments (Table 1.3-1).

1) Patient has received onabotulinumtoxin A for migraine or for any medical or cosmetic reason requiring injection in the head, face, or neck within 4 months prior to Visit 1/Screening.
2) Patient is using medication containing opioids (including codeine) or barbiturates (including butalbital/aspirin/caffeine, butalbital/paracetamol/caffeine, or any other combination containing butalbital) on more than 4 days during the screening period for the treatment of migraine or for any other reason.
3) Patient has used an intervention/device (eg, scheduled nerve blocks or transcranial magnetic stimulation) for migraine within 2 months prior to Visit 1/Screening.
4) 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.
5) Hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease considered clinically significant in the judgment of the investigator
6) 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
7) History of 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, considered clinically significant in the judgment of the investigator

8) Known infection or history of human immunodeficiency virus (HIV), tuberculosis, or hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
9) Past or current history of cancer in the past 5 years, except for appropriately treated skin carcinoma other than malignant melanoma
10) History of hypersensitivity reactions to injected proteins, including monoclonal antibodies
11) 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
12) Prior exposure to a monoclonal antibody targeting the CGRP pathway meeting the following conditions:
    - Less than 5 months has passed since the final administration of AMG334, LY2951742, or ALD403.
    - Less than 1 year has passed since the final administration of TEV-48125 (PFS). (Even if 1 year has passed since the final administration, patient cannot be enrolled if assessment of anti-drug [TEV-48125] antibody [ADA] due to the previous administration is positive or inconclusive.)
13) Any finding in the screening or baseline 12-lead electrocardiogram (ECG) considered clinically significant in the judgment of the investigator
14) Any finding that, in the judgment of the investigator, is a clinically significant abnormality, including in chemistry, hematology, coagulation, and urinalysis test values
15) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (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
16) Serum creatinine more than 1.5 × ULN, clinically significant proteinuria, or evidence of renal disease at screening
17) History of alcohol or drug abuse during the past 2 years, or alcohol or drug dependence during the past 5 years
18) Females who are breast-feeding at the time informed consent is obtained and/or who have a positive pregnancy test result at screening or baseline
19) Sexually active males or females of childbearing potential (FOCBP) who do not agree to practice 2 different methods of birth control or remain abstinent during the trial 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, intrauterine device, oral contraceptive, condom (all of which are approved or certified in Japan).
20) The patient cannot participate or successfully complete the trial for other reasons in the opinion of the investigator.

A definition of childbearing potential can be found in Section 10.3.

Subjects must agree to restrictions to medications described in Section 6.5.1 and Section 6.5.2.

[Rationales for exclusion criteria]

1) through 4): These criteria were set to appropriately evaluate efficacy.

5) through 9), 11), 17), and 20): These criteria were set to appropriately evaluate efficacy and safety.

10) and 13) through 16): These criteria were set to appropriately evaluate safety.

12): This criterion was set in consideration of the potential effect on the measurement of blood concentration of the drug.

18) and 19): These criteria were set because the safety of the IMP in pregnant or nursing females had not been established.

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

Not applicable.

5.3.2 Caffeine, Alcohol, and Tobacco

Not applicable.

5.3.3 Activity

Not applicable.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and who signs an informed consent form (ICF), but who is judged to be ineligible based on the inclusion and exclusion criteria.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of informed consent
- Visit date (screening visit)

- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Height and weight
- eDiary
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

Subjects who sign an ICF but who are judged to be ineligible based on the inclusion and exclusion criteria are permitted to be re-screened. In the event that the subject is re-screened for trial participation, a new ICF must be signed, and a new subject identification number must be assigned to the subject prior to performing the rescreening examination.

6 Trial Treatments

6.1 Trial Treatments Administered

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

Prior to administration, the IMP is to be removed from the refrigerator and left to stand at room temperature for 30 minutes. The IMP can be used for up to a cumulative total of 8 hours after it has reached room temperature.

For the self-administration procedure and the treatment period, see Section 4.1.

6.1.1 Visit 2/Baseline: Self-administration at the Trial Site

- By Visit 2/Baseline, the investigator will instruct the subject on self-administration via the AI using the "Procedure for TEV-48125 AI Self-administration."
- Using a check sheet, the investigator will determine whether self-administration at the trial site is possible.
- Subjects for whom the investigator judges self-administration to be possible will perform self-administration at the trial site under the supervision of the investigator.
- Using a check sheet, the investigator will confirm the execution status of self-administration, the subject's compliance with the self-administration procedure,

and any deficiencies with the AI device, and judge whether self-administration at home is possible.

6.1.2 Visit 3: Self-administration at Home

- When the subject visits the trial site for Visit 3, the investigator will instruct the subject on IMP handling and the self-administration procedure and use a check sheet to reconfirm that self-administration at home is possible.
- Subjects for whom the investigator judges self-administration at home to be possible will perform self-administration at home according to the "Procedure for TEV-48125 AI Self-administration."
- After self-administration at home the subject will use a check sheet to record the execution status of self-administration at home, compliance with the procedure for self-administration, any injection site reaction, and any deficiencies with the AI device, and submit the check sheet to the investigator at the next trial site visit.
- When the subject visits the trial site for PK blood sampling (PK visit 2), the investigator will review the check sheet recorded by the subject and conduct an interview to confirm the execution status of self-administration at home, the subject's compliance with the self-administration procedure, and any deficiencies with the AI device.

6.1.3 Information Regarding Trial Treatment Administration

The investigator will record the date and time of IMP self-administration and the injection site in the eCRF. The amount of drug solution remaining in the AI and any leakage of drug solution on the skin after subcutaneous injection will be recorded based on the following criteria, as information regarding the amount of IMP administered.

[Amount of drug solution remaining in the AI]

Check the plunger viewing window to confirm whether or not all of the drug solution has been injected and select the appropriate description of the amount of drug solution remaining from the following 0 to 4.

0 → All drug solution has been injected

1 → Approximately 1/4 of the drug solution remaining

2 → Approximately 1/2 of the drug solution remaining

3 → Approximately 3/4 of the drug solution remaining

4 → Almost all of the drug solution remaining

[Leakage of drug solution on the skin after subcutaneous injection]

Observe the injection site for any leakage of the drug solution and select the appropriate description from the following 0 to 4.

0 → No sign of drug solution on the skin

1 → Slight wetness on the skin (mist)

2 → Approx. 1/5 (0.3 mL) of the drug solution observed on the skin (most of the drug solution subcutaneously administered)

3 → Approx. 1/2 (0.75 mL) of the drug solution observed on the skin (ie, approx. 1/2 of drug solution subcutaneously administered)

4 → Almost all of the drug solution observed on the skin (ie, little or no drug solution subcutaneously administered)

If any deficiencies are found with the AI device provided to the subject, the following information are to be recorded in the eCRF.

[Status of problem with AI device]

- Description of problem
- Date on which problem was observed
- Lot No.
- Whether or not self-administration was performed using this AI device
- Occurrence of any AEs related to the deficiency with the AI device

Any deficiencies with the AI device should be reported as specified in Section 6.2.5 "Reporting of Product Quality Complaints."

6.1.4 Medical Devices

In this trial, the injector prefilled with TEV-48125 (combination product of TEV-48125 and AI) will be handled as the IMP. The administration method is described in Section 6.1, Trial Treatments Administered.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the fremanezumab (TEV-48125) IB.

The IMP is a combination product. Each AI for single-use administration contains TEV-48125 225 mg/1.5 mL (150 mg/mL).

The investigator will provide the IMP only to the subjects considered able to perform self-administration at home and instruct them on how to handle the IMP according to the protocol-specified procedure.

Unused IMPs will be collected by the sponsor and used IMPs will be discarded at the trial site.

6.2.1 Packaging and Labeling

The IMP will be provided to the person in charge of IMP management (IMP manager) by the sponsor or designated agent. The IMP will be supplied as packages each containing one AI prefilled with TEV-48125. Each package used in the dosing period will be labeled to clearly disclose the compound code, protocol number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager.

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

The clinical site staff will maintain a temperature log in the IMP storage area to record the temperature.

For self-administration at home, the subject will take home the IMP in a cool bag and store it in the refrigerator, avoiding freezing.

6.2.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, and returned. The IMP manager must not provide the IMP to any subject not participating in this protocol.

6.2.4 Returns and Destruction

Subjects must return unused or used IMP to the trial site.

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

6.2.5 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:

- Malfunction/failure 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

6.2.5.1 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) (destination's e-mail address: IRE_PQC_406-102-00005@otsuka.jp) by e-mail immediately after becoming aware of the PQC of the information indicated in Section 6.2.5.2, Information Required for Reporting Product Quality Complaints.

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

PQCs relating to the occurrence of or the risk of causing a serious adverse event due to deficiency with the AI device will be handled as immediately reportable events (IREs) in accordance with Section 8.9.3, Immediately Reportable Events, and only PQCs relating to the occurrence of a serious adverse event will be handled in accordance with Section 8.9.2, Eliciting and Reporting Adverse Events.

A deficiency with the AI device (AI device deficiency) is defined as any defect in the quality, safety, or performance of the device, such as mechanical breakage and malfunction, no matter whether it is caused by design, manufacture, dispensing, storage, or use.

6.2.5.2 Information Required for Reporting Product Quality Complaints

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

6.2.5.3 Return Process in Reporting Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. The sponsor may indicate the procedure for returning the sample, as appropriate.

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

6.2.5.4 Assessment/Evaluation

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

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial.

6.4 Subject Compliance

Prior to performing self-administration at the trial site and home, the subject will be given instructions on the self-administration procedure by the investigator using “Procedure for TEV-48125 AI Self-administration.” The subject must fully understand the procedure before performing self-administration according to the “Procedure for TEV-48125 AI Self-administration.” After self-administration at home, the subject will use a check sheet to record the execution status of self-administration at home, any injection site reaction and its severity, compliance with the self-administration procedure, and any deficiencies with the AI device, and submit the check sheet to the investigator at the next trial site visit.

The subject will appropriately store the IMP according to the storage method specified in “Procedure for TEV-48125 AI Self-administration.” In the event that the IMP has not been stored as specified or any IMP defect has been found, the subject will promptly notify the person in charge at the trial site and will be given an instruction about how to

deal with the situation, such as replacing the IMP. If the subject decides to change the scheduled date of self-administration, the subject will promptly notify the investigator.

6.5 Concomitant Medications or Therapies

The investigator will record all medications and therapies taken by the subject from 5 months before the start of IMP administration (Visit 2/Baseline) through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and exploratory objectives) on the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication name, purpose of use, dose per administration, frequency, route of administration, start date and end date of administration. For concomitant therapy, the following will be recorded in the eCRF: therapy name, purpose of use, start date and end date.

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 6.5.1-1 or Table 6.5.2-1 are allowed.

6.5.1 Prohibited Medications (Preventive Migraine Medications)

Use of any preventive migraine medications other than the IMP (see Table 6.5.1-1) will be prohibited.

Table 6.5.1-1 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 if given as a topical preparation or eye drops.

6.5.2 Restricted Concomitant Medications (Preventive Migraine Medications)

Subjects will be allowed to use no more than 2 concomitant preventive migraine medications (see Table 6.5.2-1) at a stable dose and regimen during the trial if the medications were previously prescribed for migraine or for another indication. However, such subjects on preventive medication must be on a stable dose and regimen for at least 2 months of consecutive use prior to screening examination (Visit 1/Screening). 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 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 screening examination (Visit 1/Screening). Subjects on such medicines or supplements should be on a stable dose and regimen in so far as possible.

Table 6.5.2-1 List of Restricted Concomitant Medications (Preventive Migraine Medications)

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

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

6.5.3 Prohibited Concomitant Therapies

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

6.5.4 Rescue Medications

Not applicable.

6.6 Intervention after the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor decides to terminate or suspend the trial for any reason, prompt notification will be given to the head of the trial site and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the institutional review board (IRB) if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The head of the trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

After being enrolled in the trial following eligibility assessment based on the inclusion and exclusion criteria, 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 continuing his/her trial participation wherever possible as described in Section 7.3.5, Procedures to Encourage Continued Trial Participation.

If any of the following withdrawal criteria is met and it is decided to discontinue treatment for a subject, the withdrawal examination specified in Section 1.3.2.5, Visit 4/End of Treatment or at Withdrawal, will be performed, and the date and reasons for discontinuation (see Section 7.3.3, Documenting Reasons for Treatment Interruption or Discontinuation) will be recorded in the source documents and eCRF.

1) The subject's (or the subject's legal representative if he/she is a minor) requests 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 Section 10.5).

4) The subject is unable to perform self-administration as determined by the investigator.
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) A significant deviation relating to IMP administration
7) A female subject becomes pregnant, or is suspected of being pregnant, or desires to become pregnant (see Section 10.3).
8) Other cases where the investigator thinks that the subject should discontinue treatment for reasons such as a difficulty in complying with the protocol

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

If any of the following criteria is met and it is decided to discontinue a subject's treatment, the investigator will perform the withdrawal examination specified in Section 1.3.2.5 and record the date and following reasons for discontinuation in the source documents and eCRF:

- The subject's (or the subject's legal representative if he/she is a minor) requests withdrawal
- AE
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard.
  - Continuing IMP administration places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to the IMP).
  - The subject meets any of the discontinuation criteria specified in the Guidance on Safety Monitoring (see Section 10.5).
- The subject is unable to perform self-administration as determined by the investigator.
  - Prior to Visit 2/Baseline (self-administration at the trial site), the investigator decides that the subject is unable to perform self-administration as specified in the procedure.
  - Following Visit 2/Baseline (self-administration at the trial site), the investigator decides that the subject is unable to perform self-administration at home as specified in the procedure.
- Protocol deviation
  - 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.
  - Noncompliance with IMP administration (including a failure to self-administer the IMP at home within the acceptable window for treatment)
- Site terminated by sponsor

- Study terminated by sponsor
- Deficiency with the AI device
- Lost to follow-up
- Pregnancy (see Section 10.3)
- Other

If the subject discontinues IMP administration due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.2, Treatment Discontinuation, must be followed.

7.3.4 Withdrawal of Consent or Assent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. 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:

- 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 records 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 their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.2, Treatment Discontinuation). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3, Documenting Reasons for Treatment Interruption or 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 methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.3.5 Procedures to Encourage Continued Trial Participation

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

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before Visit 4/End of treatment during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

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

If the subject is classified as “lost to follow-up,” “Were you able to contact the subject?,” “Date of contact/Date of final contact attempt,” and “Contact method” will be recorded in the source documents and eCRF.

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Section 1.3, Schedule of Assessments.

8.1 Efficacy Assessments

Efficacy parameters will be evaluated, as exploratory endpoints, based on the following headache information collected from the eDiary:

- Number of migraine days
- Number of headache days
- Number of headache days of at least moderate severity

8.2 Pharmacokinetic Assessments

For safety reasons, this trial will analyze plasma drug concentrations after self-administration for a marked decrease or increase.

8.2.1 Plasma Drug Concentrations

Blood samples (6 mL) will be collected via venipuncture in vacutainers containing dipotassium ethylenediaminetetraacetic acid (EDTA) and processed into plasma to determine the concentrations of TEV-48125. Additional metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, samples for determination of drug concentrations may be used for the investigation of a bioanalytical method, if needed.

Blood samples for determination of drug concentrations will be collected at the time points as shown in Table 1.3-1 (schedule of assessments).

Blood sampling status for determination of drug concentrations and the actual date and time of blood sampling will be recorded in the eCRF. The results of measurements will be reported directly to the sponsor from the bioanalytical laboratory; therefore, recording of the results in the eCRF is not needed.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Operations Manual.

Plasma samples will be shipped to the bioanalytical laboratory for analysis. Additional information will be provided in the Operations Manual.

8.3 Immunogenicity Assessments

8.3.1 Serum Samples for Immunogenicity Assessments

Blood samples (5 mL) will be collected via venipuncture in vacutainers not containing anticoagulant (but containing procoagulant) and processed into serum to analyze ADA.

Blood samples for immunogenicity assessment will be collected at the time points as shown in Table 1.3-1 (schedule of assessments).

Blood sampling status for immunogenicity assessment and the actual date and time of blood sampling will be recorded in the eCRF. The results of analysis will be reported directly to the sponsor from the ADA analytical laboratory; therefore, recording of the results in the eCRF is not needed.

After processing into serum, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Operations Manual.

Serum samples will be shipped to the ADA analytical laboratory for analysis. Additional information will be provided in the Operations Manual.

8.4 Pharmacodynamic Assessments

Not applicable.

8.5 Pharmacogenomic Assessments

Not applicable.

8.6 Biomarker Assessments

Not applicable.

8.7 Future Biospecimen Research Samples

Not applicable.

8.8 Safety Assessments

8.8.1 Adverse Events

In this trial, AEs related to TEV-48125 as well as those related to the AI device (ie, AEs attributable to device manipulation during self-administration or to the AI device itself) will be collected.

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.9, Adverse Events.

8.8.2 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments. The total volume of blood to be collected for each subject is 87 mL, including 15 mL (5 mL × 3) for serum ADA assessment and 24 mL (6 mL × 4) for determination of plasma drug concentrations in addition to blood samples for clinical laboratory tests.

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 assess the eligibility of each subject based on clinical laboratory values measured by the central laboratory.

Any additional clinical laboratory tests, if required apart from those performed at scheduled time points of blood/urine collection for reasons such as AEs, will also be performed by the protocol-specified central laboratory. Samples will be collected, treated, stored, and shipped as described in a separate operational procedure.

For WOCBP, a urine or serum pregnancy test (hCG test) will be performed. If a urine test at screening is positive, an hCG test will be performed with a serum sample collected for biochemistry during screening.

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

8.8.3 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1). In the 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 in so far as possible. On the eCRF, the date and results of assessments will be recorded at Visit 1/Screening, and only the date of assessments will be recorded at Visit 2/Baseline

and subsequent visits. Any clinically significant physical finding that is not observed at Visit 1/Screening but seen at Visit 2/Baseline or any later visit will be considered an AE, recorded in the source documents and eCRF, and monitored until its outcome has been sufficiently evaluated.

8.8.4 Vital Signs

Vital signs will be collected at the time points described in the schedule of assessments (Table 1.3-1). Before blood pressure and pulse rate are measured, subjects must remain at rest in a sitting, supine, or standing position for at least 5 minutes. Subjects should be monitored for potentially clinically significant vital sign values. Date of measurement, body position, body part, systolic and diastolic blood pressures (integer; mmHg), pulse rate (integer; beats/min), temperature (up to one decimal place; °C), and respiratory rate (integer; breaths/min) will be recorded in the eCRF. 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.

8.8.5 Electrocardiogram

Electrocardiograms will be performed at the time points described in the schedule of assessments (Table 1.3-1). Electrocardiograms will be performed with a 12-lead ECG provided by the sponsor-selected central laboratory after the subject has rested in a supine position for at least 5 minutes. Electrocardiograms will be measured and transmitted to the protocol-selected central laboratory in accordance with a separate operational procedure. Any unscheduled ECGs must also be transmitted to the designated central laboratory. The central laboratory will report interpretations to the investigator, who will then review the interpretations promptly and date and sign the ECG report as an official document.

The investigator will clinically assess the ECG results. Subjects should be monitored for potentially clinically significant ECG results. The date of ECG measurement and the investigator's interpretation will be recorded in the eCRF. The central ECG results and interpretations will be reported directly to the sponsor from the central laboratory via electronic file transfer; therefore, recording of the results and interpretations in the eCRF is not needed.

8.8.6 Suicidality Monitoring

8.8.6.1 Columbia-Suicide Severity Rating Scale

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1). The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess the subject's suicidal ideation/suicidal behavior, intensity, and frequency. This scale consists of the C-SSRS Baseline Version, which assesses a lifetime history of suicide-related events and suicidal ideation, and the C-SSRS Since Last Visit Version, which focuses on suicidality since the last visit (see Section 10.6 and Section 10.7). The C-SSRS Baseline Version will be completed at Visit 2/Baseline and the C-SSRS Since Last Visit Version will be completed at all subsequent visits. The date and results of assessment will be recorded in the source documents and eCRF.

The subject will answer "yes" or "no" to suicidal ideation questions 1 and 2. If the answer to question 2 is "yes," then the subject will also answer suicidal ideation questions 3 through 5. If the answer to either question 1 or 2 is "yes," the intensity of suicidal ideation will also be assessed. For the intensity of suicidal ideation, frequency and duration will be rated on a scale of 1 to 5, and controllability, deterrents, reasons for ideation will be rated on a scale of 0 to 5.[15]

The subject will also answer "yes" or "no" to the suicidal behavior questions shown below. If the answer to any question is "yes," a more detailed answer will be requested and assessed. The total number of each actual, interrupted, or aborted attempts will be recorded.

If the subject actually attempted suicide, actual lethality/medical damage will be rated on a scale of 0 to 5. If the actual lethality/medical damage is rated 0, then potential lethality will be rated on a scale of 0 to 2.

Suicide ideation:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent

Suicidal behavior:

Actual attempt, self-injurious behavior without suicidal intent, interrupted attempt

Aborted or self-interrupted attempt, preparatory acts or behavior, suicidal behavior, completed suicide (the Since Last Visit version only)

8.8.7 Other Safety Variables

8.8.7.1 Height and Weight

Height and weight will be measured at the time points described in the schedule of assessments (Table 1.3-1) and BMI will be calculated. Weight will be measured while minimizing fluctuations associated with clothing. Date of measurement, height, and weight will be recorded in the eCRF. Any height/weight measured up to more than one decimal place will be rounded to one decimal place.

8.8.7.2 Injection Site Reaction Assessment

Injection site reaction will be assessed at the time points described in the schedule of assessments (Table 1.3-1). Injection site reaction assessments will occur immediately and 1 hour after each IMP administration. When the IMP is self-administered at home, the subject will self-assess and record injection site reactions immediately and 1 hour after IMP administration. At a later visit, the investigator will assess injection site reactions based on the record of the subject's self-assessment and medical interview with the subject.

The injection site(s) will be observed 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, or grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after completion of IMP administration, the subject will be monitored for hourly reassessment thereafter until the reaction/pain is of moderate or less severity. For self-administration at home, injection site reaction/pain will also be recorded hourly until reaction/pain is of moderate or less severity.

- Injection-site erythema, induration, and ecchymosis will be graded as follows: Absent, 5 to ≤ 50 mm (mild), > 50 to ≤ 100 mm (moderate), and > 100 mm (severe). Induration must be assessed by careful superficial palpation while avoiding placing pressure on or squeezing the injection site.
- Injection-site pain will be evaluated according to Table 8.8.7.2-1.

The date and time and results of injection site assessment will be recorded in the eCRF, and an injection site reaction (mild, moderate, severe, or worst possible) will be reported as an AE. Needle puncture-related pain will not be assessed or considered an AE.

Table 8.8.7.2-1 Severity Grading of Pain for Injection Site Assessment	
Grade	**Assessment**
0	No pain
1	Mild
2	Moderate
3	Severe
4	Worst possible

8.9 Adverse Events

8.9.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned 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.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of treatment. In more detail, TEAEs are all adverse events which started after the start of IMP treatment; or if the event was continuous from baseline and was worsening after the start of IMP treatment.

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 inpatient 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 nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- 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.

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

Immediately Reportable Event (IRE):

- Any SAE.
- Possibility of developing into an SAE (ie, An observed deficiency with the AI device, though not causing an SAE at the moment, may possibly develop into an SAE. Where the possibility exists that an SAE may develop, this must be reported, using the IRE form, to the sponsor as described in Section 6.2.5, Reporting of Product Quality Complaints. It will be recorded on the AE eCRF only if an AE occurs.)
- Any adverse events of special interest (AESIs) (ie, any ophthalmic AE of at least moderate severity and any event of suspected anaphylaxis or severe hypersensitivity reaction).
- Any AE related to occupational exposure (any AE related to handling of the IMP affecting the investigator or trial personnel [eg, dacryorrhea occurring in a nurse who has accidentally spilt/splashed an injection drug and its droplets have entered his/her eye(s).])
- Potential serious hepatotoxicity (see Section 8.9.6).
- 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 and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE eCRF if there is an abnormality or complication. This includes pregnancy of the subject or the partner of the subject.
- All infections: Only cases of suspected contamination of biological IMPs with pathogens, including HBV, HCV, HIV, and the like. 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 laboratory tests for each individual subject as they become available. This review will be documented by the investigator's dated signature on the laboratory report. 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 (ie, clinically significant) 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 eCRF. The severity 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.

TEV-48125 Causality: Assessment of causal relationship of an AE to the use of TEV-48125 is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between TEV-48125 and the AE.

Not Related: There is no temporal or causal relationship between TEV-48125 and the AE.

AI Device Causality: Assessment of causal relationship of an AE to the use of the AI device is defined as follows:

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

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

Manipulation Causality: Assessment of causal relationship of an AE to the manipulation is defined as follows:

Related: There is a reasonable possibility of a temporal and causal relationship between subject's manipulation and the AE.

Not Related: There is no temporal or causal relationship between subject's manipulation and the AE.

8.9.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading 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 eCRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF.

Medical terminology should be used for 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.

In addition, the sponsor must be notified immediately by e-mail in principle of any IREs according to the procedure outlined below, in Section 8.9.3, Immediately Reportable Events. Special attention should be paid to recording hospitalization and concomitant medications.

See Section 6.2.5, Reporting of Product Quality Complaints, for the procedure for reporting AI device deficiencies that have not caused SAEs or are unlikely to cause SAEs. Any AI device deficiency that has caused or may cause an SAE must be handled as an IRE in accordance with Section 8.9.3, Immediately Reportable Events.

Adverse event, start date, end date, seriousness, severity, relationship to TEV-48125 treatment (TEV-48125 Causality), relationship to AI device (AI Device Causality), relationship to the subject's manipulation (Manipulation Causality), action taken with trial treatment and outcome will be recorded on the source documents and in the eCRF.

8.9.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after the investigator or site personnel becomes aware of any IRE (see Section 8.9.1, Definitions), by e-mail in principle to the sponsor or designee using the contact information on the cover page of this protocol (Please note that the IRE form is NOT the AE eCRF.). When sending an IRE form by e-mail, etc, sufficient care and attention must be taken to protect subject privacy.

8.9.4 Medical Device Incidents (Including Malfunctions)

In this trial, the injector prefilled with TEV-48125 (combination product of TEV-48125 and AI) will be handled as the IMP. However, the "status of deficiencies with AI device" and "AI Device Causality" of AEs will also be investigated in the trial (see Section 6.1.3, Information Regarding Trial Treatment Administration, and Section 8.9.1, Definitions).

8.9.5 Adverse Events of Special Interest

Adverse events of special interest are defined below. These will be immediately reported to the sponsor as IREs according to the procedure outlined in Section 8.9.3, Immediately Reportable Events.

- Any ophthalmic AE of at least moderate severity
- Any event of suspected anaphylaxis or severe hypersensitivity reaction

In response to the finding of mild ciliary periarteritis in monkeys treated with TEV-48125 in a 3-month multiple-dose toxicity study, ophthalmic AE was addressed as an AESI in 3 multinational phase 3 trials (Trials TV48125-CNS-30049, TV48125-CNS-30050, and

TV48125-CNS-30051). These trials demonstrated neither clinically significant differences from placebo nor TEV-48125-related abnormal patterns. Three ongoing Korean and Japanese trials (Trials 406-102-00001, 406-102-00002, and 406-102-00003) are also addressing ophthalmic AE as an AESI. In line with this approach, the present trial will handle ophthalmic AE in the same way.

Severe hypersensitivity reaction will be monitored using the clinical criteria for diagnosing anaphylaxis[16] proposed in the second symposium on the definition and management of anaphylaxis hosted by National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network in 2006 (see Section 10.8). If anaphylaxis is suspected, vital signs (eg, oxygen saturation and respiratory rate) will be measured. If severe hypersensitivity reaction (eg, anaphylaxis) is suspected, ADA will be assessed. The investigator may perform other assessments at his/her discretion and decide whether or not to continue the subject's trial participation. If it is decided to discontinue the trial, necessary actions will be taken in accordance with Section 7.3.2, Treatment Discontinuation.

8.9.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥2 times the ULN, complete an IRE form with all values listed and also report as an AE on the eCRF.

8.9.7 Procedure for Breaking the Blind

This trial will not use blinding procedures.

8.9.8 Follow-up of Adverse Events

8.9.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

8.9.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to 28 days after the last dose of IMP is administered.

Immediately reportable events that are identified up to the last schedules contact or ongoing at the last scheduled contact must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a subject's last scheduled contact (up to last subject last visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.9.3, Immediately Reportable Events.

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. The investigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- The subject is lost to follow-up, or
- Has died.

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. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.9.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs which are reported to the investigator after 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 according to the procedures outlined in Section 8.9.3, Immediately Reportable Events. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and any significant follow-up information should continue to be reported to the sponsor until the events have resolved or stabilized, or the subject is lost to follow-up or has died.

8.10 Treatment of Overdose

For treatment of overdose, please refer to IB Section 7.6, Overdosage.

There is no TEV-48125-specific antidote for overdosage. Overdosage should be treated with symptomatic therapies and common supportive care.

8.11 Subject Assessment Recording

8.11.1 Electronic Headache Diary

Headache-related efficacy endpoints will be derived from headache data collected using an eDiary. At Visit 1/Screening, eligible subjects will receive comprehensive training from trial personnel on the use of the eDiary. On each day, the subject will be asked to enter headache data in the eDiary 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 eDiary no later than 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. The subject should enter headache information into the eDiary on at least 75% of the days between the scheduled visits.

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.

8.11.2 Recording Information on Self-administration at Home

The subject will assess and record in a check sheet the execution status of self-administration at home, his/her compliance with the specified procedure, and presence or absence of deficiencies with the AI device. Any injection site reaction will also be recorded in the check sheet. The completed check sheet will be submitted to the investigator.

8.12 Other Assessments

8.12.1 Assessment of Self-administration at Home

The following information will be collected to facilitate a comprehensive evaluation of the feasibility of AI-assisted self-administration of TEV-48125 at home.

- Execution status of self-administration at home
- Subject compliance with the self-administration procedure

Any deficiencies with the AI device will also be assessed.

9 Statistical Considerations

9.1 Sample Size

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

9.2 Datasets for Analysis

The safety dataset includes all subjects that were administered at least one dose of IMP.

The efficacy dataset includes all subjects who were administered at least one dose of IMP and have eDiary data for efficacy evaluation at baseline and for at least 10 days after baseline.

9.3 Handling of Missing Data for Primary Endpoint Analysis

Missing data will not be imputed.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

Efficacy analysis is described in Section 9.4.3.7, Exploratory Endpoint Analysis.

9.4.2 Safety Analysis

The safety dataset will be used in safety analysis.

9.4.2.1 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 overall, by self-administration at the trial site, and by self-administration at home:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to TEV-48125
- TEAEs potentially causally related to AI device
- TEAEs potentially causally related to subject's manipulation
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

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

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

9.4.2.3 Deficiencies With the Autoinjector Device

Deficiencies with the AI device will be listed.

9.4.2.4 Clinical Laboratory Data

For each laboratory parameter (excluding qualitative urinalysis), descriptive statistics will be calculated for measurements and changes from baseline at each time point (including final assessment). The central laboratory reference ranges will be used to group measurements into "below the reference range," "within the reference range," or "above the reference range" and a shift table from baseline will be provided.

For each qualitative laboratory parameter, a shift table from baseline will be provided.

9.4.2.5 Physical Examination and Vital Signs Data

Physical examination findings will be listed.

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

9.4.2.6 Electrocardiogram Data

For each ECG parameter, descriptive statistics will be calculated for measurements and changes from baseline at each time point (including final assessment).

For the normality/abnormality judgment, a shift table from baseline will be provided.

For QT corrected by Fridericia's formula (QTcF), the number and proportion of subjects where the measured QTcF after the start of IMP administration is > 450 msec,

> 480 msec, and > 500 msec will be determined. The number and proportion of subjects with changes from baseline in the QTcF of > 30 msec and > 60 msec will also be determined.

9.4.2.7 Other Safety Data

9.4.2.7.1 Weight

Descriptive statistics will be calculated for measurements and changes from baseline at each time point (including final assessment).

9.4.2.7.2 Injection Site Reactions

Frequency distributions will be calculated for severity of injection site reactions (erythema, induration, ecchymosis, and pain) at each time point.

9.4.2.7.3 Columbia-Suicide Severity Rating Scale

Subjects with suicidal ideation or suicidal behavior will be listed.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

For demographic and baseline characteristics in each analysis set, frequency distributions or descriptive statistics will be calculated depending on the nature of the data.

9.4.3.2 Pharmacokinetic Analysis

No pharmacokinetic analysis is planned.

9.4.3.3 Pharmacodynamic Analysis

No pharmacodynamic analysis is planned.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No pharmacokinetic/pharmacodynamic analysis is planned.

9.4.3.5 Immunogenicity

9.4.3.5.1 Immunogenicity Analysis

The frequency of ADA expression in the safety dataset will be calculated.

9.4.3.6 Pharmacogenomic Analysis

No pharmacogenomic analysis is planned.

9.4.3.7 Exploratory Endpoint Analysis

Descriptive statistics will be calculated for the number of migraine days per month (28 days) in 8 weeks after the first dose of IMP and the number of migraine days per month

in 4 weeks after each dose as well as their respective changes from baseline in the efficacy dataset. The number of headache days of at least moderate severity and the number of headache days will also be analyzed in the same manner.

The proportion of subjects who achieved a 50% or greater reduction in the number of migraine days per month in 8 weeks after the first dose of IMP and the proportion of subjects who achieved a 50% or greater reduction in the number of migraine days per month in 4 weeks after each dose will be calculated. The number of headache days of at least moderate severity will also be analyzed in the same manner.

9.4.3.8 Plasma Drug Concentrations

Descriptive statistics will be calculated for measurements at each time point for blood sampling for determination of plasma drug concentrations. A box plot and a scatter plot will be provided for each measurement.

9.5 Interim Analysis and Adaptive Design

No interim analysis or adaptive design is applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, International Council for Harmonisation (ICH) GCP: Consolidated 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 by an IRB according to regional requirements, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and handling eCRF, IRE form, etc, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject identifier (ID) will be used to identify each subject.

Financial aspects, insurance coverage for subjects, etc, and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH GCP: Consolidated Guideline E6 and local regulatory requirements. In support of the site's standard process for administering informed consent, this trial will also allow for electronic informed consent (eICF) as a tool within applicable regions and trial sites. The eICF utilizes the IRB-approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

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-approved written ICF will be signed and dated by both the subject and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The subject will receive 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 and the changes to the protocol results in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial and up to 225 days after the final dose of IMP may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

If a potential subject is a minor, voluntary, written informed consent will be 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 level of understanding and then sign and date the ICF himself or herself.

10.1.3 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 ID in eCRF. 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.

10.1.4 Quality Control and Quality Assurance

The sponsor will implement the trial-related quality management activities in accordance with ICH E6 (R2). The details of the quality management activities are separately described in the quality management plan.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH GCP: Consolidated Guideline (E6), 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 site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 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 a review of the eCRF with source documents, as applicable. The investigator agrees to participate with audits.

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

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, subject enrolled in violation of eligibility criteria, prohibited/restricted medication criteria, or prohibited therapy criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject’s continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 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, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the trial site and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. Information on drug concentration determination and ADA analysis (eg, original reports, measurement data) will be stored at the bioanalytical laboratory and the ADA analytical laboratory. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. 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 the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC)

system that is 21 CRF Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Data entered into the eDiary by the subject will be transferred to the EDC system and included in the eCRF. Data entries and transfer will also be captured by an automatic audit trail. Data entered in the eDiary cannot be changed.

Electronic data not included in the eCRF, such as data received from central laboratories and central ECG readers, will be reconciled using key data fields by the sponsor or the contract research organization with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

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

10.1.6.4 Records Retention at the Trial Site

The trial site will maintain all documents and records pertaining to the trial for the longer of the following 2 periods. If the sponsor needs a longer retention period than either of those specified below, the trial site will discuss with the sponsor the period and method of retention.

- A period of at least 2 years after the date on which approval to market the drug is obtained. However, if the development of the drug is discontinued or if the trial site is notified that the results of the trial will not be included in the application dossier for marketing approval, a period of at least 3 years after the date on which discontinuation of drug development is decided or the trial site is notified that the trial results will not be included in the application dossier.
- A period of at least 3 years after the trial is discontinued or completed.

The trial site 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 trial site 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.

10.1.6.5 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.

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

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin (Hb) Hematocrit (Hct) Erythrocytes count (RBC) Erythrocyte indices Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Red cell distribution width (RDW) Leukocytes count (WBC) with differential count (absolute values and percentages) Neutrophils (Neu) Lymphocytes (Lym) Eosinophils (Eos) Monocytes (Mon) Basophils (Bas) Platelet count (PLT) Urinalysis: Specimen appearance Color Occult blood Glucose Microscopic analysis (high powered field) Bacteria Leukocytes count Erythrocytes count Casts Crystals pH Protein Specific gravity Albumin (ALB) Ketones Leukocyte esterase Nitrite Direct bilirubin	Serum Chemistry: Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Total bilirubin Direct bilirubin Indirect bilirubin (calculated) Urea nitrogen (BUN) Uric acid (UA) Calcium (Ca) Creatinine (Cr) Gamma glutamyl transferase (GGT) Glucose (casual) Lactic dehydrogenase (LDH) Potassium (K) Total protein Sodium (Na) Phosphorus Chloride (Cl) Carbon dioxide Magnesium Albumin Creatine phosphokinase Coagulation Prothrombin time (PT) Partial thromboplastin time (PPT) International normalization ratio (INR) Additional Tests: Urine (or serum) hCG test for FOCBP (If the result of urine hCG test is positive at screening, serum hCG test will be performed for confirmation.)

RBC = red blood cell; WBC = white blood cell.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of child-bearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

For males and FOCBP, who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control or remains abstinent) to prevent pregnancy during the course of the trial and for 225 days after the last dose of IMP. Unless the subject is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchidectomy) or remains abstinent for 225 days after the last dose of IMP, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, or condom (all of which are approved or certified in Japan). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF. Male subjects must also agree not to donate sperm from trial screening through 225 days after the last dose of IMP.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening and at each trial site visit on all FOCBP. If a urine test is positive at screening, a serum hCG test will be performed using serum samples obtained for clinical chemistry at screening examination.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that she might be pregnant (eg, missed or late menstrual cycle).

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). 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. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 225 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

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 the Pregnancy Surveillance Form(s), 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 date of birth.

10.4 Appendix 4: ICHD-3 beta Diagnostic Criteria

For further details, refer to Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, third edition ©International Headache Society 2018.

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 3 of the following 6 characteristics:
   - at least one aura symptom spreads gradually over ≥ 5 minutes
   - two or more aura symptoms occur in succession
   - each individual aura symptom lasts 5 to 60 minutes
   - at least one aura symptom is unilateral
   - at least one aura symptom is positive
   - the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis

10.5 Appendix 5: 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.[b] 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 8.8.2, 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 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 eosinophil count], and INR). The investigator should also question the patient regarding symptoms.

[b] 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.

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 antibody), 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 at least once monthly.

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.

10.6 Appendix 6: Columbia-Suicide Severity Rating Scale (Baseline)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

10.7 Appendix 7: Columbia-Suicide Severity Rating Scale (Since Last Visit)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.8 Appendix 8: 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 mmHg 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. Ann Emerg Med. 2006;47(4):373-80.

10.9 Appendix 9: Abbreviations

Abbreviation	Definition
ADA	Antidrug antibody
AI	Autoinjector
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Bas	Basophil
BMI	Body mass index
BUN	Blood urea nitrogen
Ca	Calcium
CBC	Complete blood count
CGRP	Calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Science
Cl	Chloride
CM	Chronic migraine
Cr	Creatinine
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EDTA	Ethylenediaminetetraacetic acid
EM	Episodic migraine
Eos	Eosinophil
GCP	Good Clinical Practice
γ-GTP	Gamma-glutamyl transpeptidase
Hb	Hemoglobin
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3	The International Classification of Headache Disorders, third edition
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHS	Headache Classification Committee of the International Headache Society
INR	International normalized ratio
IRB	Institutional review board

Abbreviation	Definition
IRE	Immediately reportable event
K	Potassium
LDH	Lactate (lactic acid) dehydrogenase
Lym	Lymphocyte
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mon	Monocyte
Na	Sodium
Neu	Neutrophil
OTC	Over-the-counter
PEF	Peak expiratory flow
PFS	Pre-filled syringe
PLT	Platelet
PPT	Partial thromboplastin time
PQC	Product quality complaint
PT	Prothrombin time
QTcF	QT corrected for heart rate by Fridericia's formula
RBC	Red blood cell count
RDW	Red cell distribution width
TEAE	Treatment-emergent adverse event
UA	Uric acid
ULN	Upper limit of normal
V	Visit
WBC	White blood cell count

10.10 Appendix 10: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB. 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, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB approval 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, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, 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 of the new ICF by the IRB, 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.

10.10.1 Protocol Amendment(s)/Administrative Change(s)

[Amendment 1] Approval Date: 16 Mar 2020

PURPOSE:

To clarify the text and revise written errors.

BACKGROUND:
Revisions were made to clarify the text and revise written errors.

MODIFICATIONS TO PROTOCOL:

Sectional Revisions:

Protocol Section	Before Revision	After Revision
1.3 Schedule of Assessments Table 1.3-1	[g]Assessment of injection site reaction will be ..., the subject will be reassessed hourly thereafter until the reaction and/or pain is of moderate or less severity. The investigator will perform the assessment using a checksheet after completion of self-administration at the trial site. [h]Women of childbearing potential only. If the result of urine hCG test at screening is positive, serum hCG will be tested to confirm that the result is negative by Visit 2/Baseline. ... [i]Inquiries about AEs will be .... At each subject visit, the investigator will perform assessment based on an interview and the information recorded by the subject. [m]Blood sampling for ADA assessment at Visit 2/Baseline will be performed before administration. ...	[g]Assessment of injection site reaction will be ..., the subject will be reassessed hourly thereafter until the reaction and/or pain is of moderate or less severity. The investigator will **perform the assessment after completion of self-administration at the trial site**. [h]Women of childbearing potential only. If the result of urine hCG test at screening is positive, serum hCG will be tested **to confirm that the result is negative**. ... [i]Inquiries about AEs will be .... **For self-administration at home, when the subject visits the trial site** the investigator will perform assessment based on an interview and the information recorded by the subject. [m]Blood sampling for **serum ADA** assessment at Visit 2/Baseline will be performed before administration. ...
6.1 Trial Treatments Administered	(the first part omitted) The IMP can be used for up to 24 hours after it has reached room temperature. (the rest omitted)	(the first part omitted) The IMP can be used **for up to a cumulative total of 8 hours** after it has reached room temperature. (the rest omitted)
6.5 Concomitant Medications or Therapies	The investigator will record all medications and therapies taken by the subject from 5 months before the screening examination (Visit 1/Screening) through the end of the evaluation period (defined as the time period during which subjects are	The investigator will record all medications and therapies taken by the subject from 5 months before **the start of IMP administration (Visit 2/Baseline)** through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and exploratory objectives) on the eCRF.

Protocol Section	Before Revision	After Revision
	evaluated for primary and exploratory objectives) on the eCRF.	
8.8.2 Clinical Laboratory Assessments	Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments. The total volume of blood to be collected for each subject is 87 mL. (the rest omitted) (the middle part omitted) For WOCBP, a urine or serum pregnancy test (hCG test) will be performed. If a urine test at screening is positive, the investigator will perform a serum hCG test for confirmation. (the rest omitted)	Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments. **The total volume of blood to be collected for each subject is 87 mL, including 15 mL (5 mL × 3) for serum ADA assessment and 24 mL (6 mL × 4) for determination of plasma drug concentrations in addition to blood samples for clinical laboratory tests.** (the rest omitted) (the middle part omitted) For WOCBP, a urine or serum pregnancy test (hCG test) will be performed. If a urine test at screening is positive, **an hCG test will be performed with a serum sample collected for biochemistry during screening.** (the rest omitted)
8.9.1 Definitions	(the first part omitted) An adverse drug reaction is any untoward and unintended response to an IMP related to any dose administered. (the rest omitted)	(the first part omitted) **An adverse reaction** is any untoward and unintended response to an IMP related to any dose administered. (the rest omitted)
10.1.1 Ethics and Responsibility	(the first part omitted) Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.	(the first part omitted) Financial aspects, **insurance coverage for subjects, etc,** and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.
10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information	(the first part omitted) A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening and at each trial site visit on all FOCBP. If a urine test is positive at screening, the investigator will follow-up with a confirmatory serum test. (the rest omitted)	(the first part omitted) A urine pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening and at each trial site visit on all FOCBP. If a urine test is positive at screening, **a serum hCG test will be performed using serum samples obtained for clinical chemistry at screening examination.** (the rest omitted)

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

11 References

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, combination product of TEV-48125 and the AI, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where TEV-48125 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, I have failed to be in compliance with the protocol in order to avoid an immediate hazards to any trial subject, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____
Principal Investigator Print Name	Trial Site
_____	_____
Signature	Date (DD Mon YYYY)

The sponsor signed this agreement electronically. The page of electronic signature is attached to this agreement.