

**Clinical Study Protocol with Amendment 02**

**A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled,  
Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens  
(Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the  
Prevention of Chronic Cluster Headache**

**Study Number TV48125-CNS-30057**

**NCT02964338**

**Protocol with Amendment 02 Approval Date: 01 May 2017**

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Prevention of Chronic Cluster Headache**

**Efficacy and Safety Study (Phase 3)**

**IND number: 129606**

**EudraCT number: 2016-003171-21**

**EMA Decision Number of Pediatric Investigation Plan: Not Applicable**

**Article 45 or 46 of 1901/2006 does not apply**

**Protocol with Amendment 02 Approval Date: 01 May 2017**

**Protocol Approval Date: 08 August 2016**

**Sponsor**

**Teva Branded Pharmaceutical  
Products R&D, Inc.  
41 Moores Road  
Frazer, Pennsylvania 19355  
United States of America**

**Information regarding clinical laboratories and other departments and institutions is  
found in [Appendix A](#).**

**Confidentiality Statement**

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Council for Harmonisation (ICH); United States (US) Code of Federal Regulations (CFR), and European Union (EU) Directives (as applicable in the region of the study); national country legislation; and the sponsor's Standard Operating Procedures (SOPs).

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## AMENDMENT HISTORY

The protocol for Study TV48125-CNS-30057 (original protocol dated 08 August 2016) has been amended and reissued as follows:

Amendment 02	01 May 2017 20 patients randomized/enrolled to date
Amendment 01	30 November 2016 No patients randomized/enrolled to date
Letter of Clarification 04	04 December 2016
Letter of Clarification 03	03 November 2016
Letter of Clarification 02	10 October 2016
Letter of Clarification 01	09 September 2016

The Summary of Changes to the Protocol includes the corresponding reason/justification for each change and is provided in Section 16.

## INVESTIGATOR AGREEMENT

**Clinical Study Protocol with Amendment 02**

**Original Protocol Dated 08 August 2016**

**IND Number: 129606; EudraCT Number: 2016-003171-21**

**EMA Decision Number of Pediatric Investigation Plan: Not Applicable**

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Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens  
(Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the  
Prevention of Chronic Cluster Headache**

**Principal Investigator:** \_\_\_\_\_

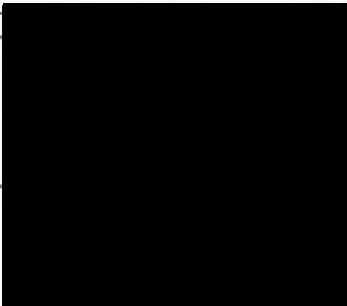

**Title:** \_\_\_\_\_

**Address of Investigational Center:** \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

**Tel:** \_\_\_\_\_

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national or local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that are furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations.

<b>Principal Investigator</b>	<b>Signature</b>	<b>Date</b>
		
<b>Sponsor's Authorized Representative</b>		<b>Date</b>
		5. 1. 2017

**COORDINATING INVESTIGATOR AGREEMENT**

**Clinical Study Protocol with Amendment 02**

**Original Protocol Dated 08 August 2016**

**IND Number: 129606; EudraCT Number: 2016-003171-21**

**EMA Decision Number of Pediatric Investigation Plan: Not Applicable**

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**A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Chronic Cluster Headache**

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes approval of this protocol and attachments, and provides assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to national and local legal and regulatory requirements and applicable regulations and guidelines.

I will make available the protocol and all information on the investigational medicinal product (IMP) that are furnished to me by the sponsor to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the IMP and the conduct of the study. I agree to keep records on all patient information, IMP shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations. In addition I will assume the responsibility of the coordinating investigator according to a separate contract.

**Coordinating Investigator:** 


**Title:** \_\_\_\_\_

**Address of Investigational Center:** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

**Tel:** \_\_\_\_\_

Coordinating Investigator	Signature	Date
		

## **CLINICAL STUDY PROTOCOL SYNOPSIS**

### **with Amendment 02**

#### **Study TV48125-CNS-30057**

**Title of Study:** A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Chronic Cluster Headache

**Sponsor:** Teva Branded Pharmaceutical Products R&D, Inc.

**Investigational New Drug (IND) Number:** 129606

**EudraCT Number:** 2016-003171-21

**EMA Decision number of Pediatric Investigation Plan:** Not applicable

**Article 45 or 46 of 1901/2006 does not apply**

**Name of Test Investigational Medicinal Product (IMP):** Fremanezumab (TEV-48125)

**EudraVigilance (EV) code for the IMP, if applicable:** SUB181665

**Type of the Study:** Efficacy and Safety Study (Phase 3)

**Indication:** Chronic cluster headache (CCH)

**Is this study conducted to investigate the New Use of an approved, marketed product?** No

**Number of Investigational Centers Planned:** Approximately 80

**Countries Planned:** Approximately 12

**Planned Study Period:** Q4/2016 (first patient in) to Q3/2018 (last patient last visit)

**Number of Patients Planned (total):** Approximately 300 patients (approximately 100 patients per treatment group) are planned to be enrolled in this study to have approximately 258 completers (approximately 86 completers per treatment group); a 14% drop-out rate is anticipated.

**Study Population:** The study population will be composed of male and female patients, 18 to 70 years of age, inclusive, with a history of CCH (as defined by International Classification of Headache Disorders, third revision beta [ICHD 3-Beta] criteria [[Headache Classification Committee of the International Headache Society \(IHS\) 2013](#)]) for  $\geq 12$  months prior to screening.

**Primary and Secondary Objectives and Endpoints:**

The primary and secondary study objectives and endpoints are as follows:

<b>Objectives</b>	<b>Endpoints</b>
<p>The <b>primary objective</b> of this study is to demonstrate the efficacy of fremanezumab in the prevention of CCH in adult patients.</p>	<p>The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data.</p>
<p>A <b>secondary objective</b> of this study is to further demonstrate the efficacy of fremanezumab in the prevention of CCH in adult patients.</p>	<p>The secondary efficacy endpoints to further demonstrate efficacy are:</p> <ul style="list-style-type: none"> <li>• the proportion of patients with a <math>\geq 50\%</math> reduction from baseline (run-in period) in the monthly average number of CH attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the first dose of the IMP, ie, based on week 0 to 4 data</li> <li>• the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data</li> <li>• the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat CCH during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• assessment of patient’s perceived improvement, as measured by the Patient-Perceived Satisfactory Improvement (PPSI) at 1, 4, 8, and 12 weeks after administration of the first dose of the IMP relative to baseline (day 0)</li> </ul>

Objectives	Endpoints
<p>A <b>secondary objective</b> of this study is to evaluate the safety of fremanezumab in adult patients with CCH.</p>	<p>The secondary safety endpoints are as follows:</p> <ul style="list-style-type: none"> <li>• occurrence of adverse events throughout the study</li> <li>• clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at each visit</li> <li>• vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.</li> <li>• 12-lead electrocardiogram (ECG) findings at screening, baseline, and week 12</li> <li>• use of concomitant medication during the study</li> <li>• clinically significant changes in physical examinations, including body weight</li> <li>• injection site reaction (ie, erythema, induration, and ecchymosis) and injection site pain assessments</li> <li>• occurrence of hypersensitivity/anaphylaxis reactions</li> <li>• suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)</li> </ul>

**Immunogenicity Assessment Objectives and Endpoints:**

The immunogenicity objective is the following:

- to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to intravenous (iv) and subcutaneous (sc) fremanezumab

The immunogenicity endpoints are the following:

- ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

**Exploratory Objectives and Endpoints:**

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in the prevention of CH in adult patients
- to explore the correlation between pharmacokinetic parameters and IMP efficacy



- to explore the relationship between biofluid biomarkers and fremanezumab concentrations
- to explore the relationship between pharmacogenetics versus headache response, CH attack characteristics, and/or safety
- to explore the relationship between soluble exploratory biomarkers versus CH response

The exploratory endpoints are as follows:

- proportion of patients with  $\geq 50\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- proportion of patients with  $\geq 75\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- proportion of patients reaching 100% reduction in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- mean change from baseline (run-in period) in the number of CH attacks during weeks 1, 2, 3, 4, 8, and 12, after administration of the first dose of the IMP
- mean change from baseline (run-in period) in the number of CH attacks during the 8-week period after administration of the first dose of the IMP, ie, based on week 0 to 8 data
- mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the second dose of the IMP, ie, based on week 4 to 8 data
- change from baseline (run-in period) in the severity of CH attacks (mild, moderate, severe, or very severe) during weeks 1, 2, 3, 4, 8, and 12 after administration of the first dose of the IMP
- mean change from baseline (run-in period) in the weekly average number of days with use of any acute headache medications during the 12-week period after administration of the first dose of the IMP, ie, based week 0 to 12 data
- total cumulative distribution of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data
- cumulative distribution function plot of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data

- mean change from baseline (run-in period) in the monthly average number of CH attacks of at least severe severity during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- changes from baseline (day 0) in responses to questionnaires that measure quality of life, satisfaction with treatment, and health status
- the relationship between biofluid biomarkers and fremanezumab concentrations
- the relationship between specific genetic polymorphisms within the calcitonin gene related peptide (CGRP) receptor-ligand complex and headache-associated genes versus headache response, specific CH attack clinical features (eg, severity, IMP effects, IMP efficacy), and/or safety (eg, adverse events to IMP)
- the relationship between baseline levels and/or mean changes in levels from baseline (day 0) in biofluid biomarkers versus treatment, CH response status (onset/duration), and response status (ie, responders versus nonresponders)

Wearable sensor substudy exploratory objectives are the following:

- to evaluate changes in sleep-wake parameters during days patients experience CH attacks relative to days free of attacks
- to evaluate changes in sleep-wake parameters in predicting seasonal onset of new CH epoch
- to evaluate changes in activity during days patients experience CH attacks relative to days free of attacks
- to determine the relationship between activity and sleep pattern and the frequency of CH attacks
- to determine the relationship between activity and sleep pattern and the intensity of CH attacks
- to determine the relationship between activity and sleep pattern and the duration of CH attacks
- to explore the differences in activity and sleep pattern in patients with CCH
- to examine the relationship between activity and sleep pattern and that of genetic and biomarker measures
- to evaluate changes in activity in predicting seasonal onset of new CH episode
- to explore the capability of predicting the onset of a new CH epoch ahead of time

Wearable sensor substudy exploratory endpoints are the following:

- change in total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency on days with and without CH attacks
- the change in the total time of sedentary, light, moderate, and vigorous activity before (6-hour period), during, and after (6-hour period) CH attack relative to days free of attacks

- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the frequency of CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache intensity during CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache duration during CH attacks
- the average total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency in patients with CCH
- the correlation between the total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the genetic and biomarker profiles
- detection of time-dependent patterns composed of lower- and higher-level activity metrics (eg, activity score and sleep/wake patterns)
- cross-correlation between the time-dependent activity patterns and CH attacks
- prediction model for the coming CH attack, intensity, and duration. The input to the prediction model (ie, features) will be selected from the measurements collected by the digital wearable devices, information collected by the self-reporting devices, and aggregated information provided by the calculated endpoints (ie, various statistics).

### **General Design:**

This is a 16-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to compare the efficacy and safety of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of CCH. The study will consist of a screening visit, a run-in period lasting approximately 4 weeks (+3 days), and a 12-week double-blind treatment period. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).

Patients will complete a screening visit (visit 1) after providing written informed consent, and eligible patients will enter a run-in period lasting at least 4 weeks (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]). Patients who had at least 10 CH attacks during the run-in period and who continue to meet eligibility criteria (including entry of CH attack information in an electronic diary, demonstrating compliance for 85% of days during the run-in period) will be randomly assigned at visit 2 (week 0) in a 1:1:1 ratio to 1 of 3 treatment groups as follows:

- fremanezumab 900-mg iv loading dose group: fremanezumab at 900 mg administered via an approximately 1-hour iv infusion at visit 2 (week 0) followed by fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively)

- fremanezumab 675-mg sc loading dose group: fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) followed by fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively)
- placebo group: placebo administered via an approximately 1-hour iv infusion and as 3 sc injections at visit 2 (week 0) followed by placebo administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively)

In order to maintain blinding throughout the study, the number of infusions and injections at each visit will be the same for all patients regardless of the treatment group to which they are randomized. Thus, all patients will receive an iv infusion of test IMP or placebo IMP followed by 3 sc injections of test IMP or placebo IMP at visit 2 (week 0), and all patients will receive single sc injections of test IMP or placebo IMP at visits 3 and 4 (weeks 4 and 8, respectively). Patients will also return for an end of treatment (EOT) visit, approximately 4 weeks after the administration of the last dose of IMP, in order to evaluate ADAs, fremanezumab concentrations, biomarkers, and safety assessments.

CH attack information will be captured daily during the double-blind treatment period using an electronic diary device. Assessments of change in quality of life and health status (using the Hospital Anxiety and Depression Scale, EuroQol-5 Dimension questionnaire, 12-Item Short-Form Health Survey, Impact on Partner and Family questionnaire, and Work Productivity and Activity Impairment questionnaire); satisfaction with treatment (using the PPSI and Patient Global Impression of Change scale); safety evaluations; blood collection for pharmacokinetic, immunogenicity, and biomarker analyses; and urine sampling for biomarker analysis will be performed at prespecified time points.

Wearable Sensor Substudy: A subset of patients in selected investigational sites will be offered the opportunity to participate in a substudy to understand the utility of physiological biomarker measures captured through wearable digital sensor devices as tools to monitor response to treatment and disease symptoms (eg, activity/sleep disruption).

**Brief Summary of Study Design for the Trial Registry(s):** This is a 16-week study to evaluate the efficacy and safety of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of CCH. Patients who provide written informed consent and complete a screening visit (visit 1) will enter a run-in period lasting at least 4 weeks (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]), and patients who continue to meet eligibility requirements will be randomized to receive test IMP (fremanezumab 900-mg iv or 675-mg sc followed by fremanezumab 225-mg sc monthly) or placebo IMP (placebo iv and sc followed by single placebo doses sc monthly). An EOT visit will occur approximately 4 weeks after the administration of the last dose of IMP to evaluate ADAs, fremanezumab concentrations, biomarkers, and safety.

Efficacy will be evaluated using CH attack data entered daily throughout the treatment period in an electronic diary and administration of questionnaires to evaluate change in quality of life, health status, and satisfaction with treatment. The safety of fremanezumab in patients with CH will be evaluated through adverse event and concomitant medication inquiries, ECGs, vital signs measurements, clinical laboratory tests, physical examinations, injection site reaction/pain

assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. In addition, blood will be collected for pharmacokinetic, immunogenicity, biomarker, and pharmacogenomic (unless not allowed per local regulation) analyses, and urine will be collected for biomarker analysis.

**Method of Randomization and Blinding:** Randomization will be performed using electronic interactive response technology (IRT). Patients will be randomly assigned with stratification based on gender, country, and baseline concomitant preventive medications (yes/no) to the fremanezumab 900-mg iv loading dose group, the fremanezumab 675-mg sc loading dose group, or the placebo group in a 1:1:1 ratio. The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses and interim analyses [by a third-party, unblinded statistician]), and patients will be blinded to treatment assignment throughout the study.

The IRT will manage initial drug supply, maintenance of adequate IMP supplies on site, and study randomization centrally. In the event that the IRT system is not functioning for emergency unblinding, the next course of action is to contact via phone the IRT on-call customer support helpline for manual emergency unblinding.

The randomization code will be generated by the IRT third-party vendor, following specifications from the Biostatistics Department. A Teva statistician will be responsible for reviewing the dummy randomization codes, and the final randomization code will be maintained by the third-party vendor in a secure location.

At the time of analysis (after the end of the study), after receiving an unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure.

**Investigational Medicinal Products: Dose, Pharmaceutical Form, Route of Administration, and Administration Rate:**

IMPs are defined as the test IMP and placebo IMP (Table 1).

**Table 1: Investigational Medicinal Products Used in the Study**

IMP Name	Test IMP	Placebo IMP
<b>Trade name and INN, if applicable, or company-assigned number</b>	Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, or RN307])	n/a
<b>Formulation</b>	Solution for injection	Solution for injection
<b>Unit dose strength(s)/Dosage level(s)</b>	225 mg/1.5 mL 900 mg iv loading dose followed by 225 mg sc monthly or 675 mg sc followed by 225 mg sc monthly	n/a
<b>Route of Administration</b>	Fremanezumab will be administered as iv infusions and sc injections by qualified study personnel at the investigational center.	Placebo will be administered as iv infusions and sc injections by qualified study personnel at the investigational center.

IMP Name	Test IMP	Placebo IMP
<b>Packaging</b>	Fremanezumab will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Prefilled syringes will contain fremanezumab at a concentration of 150 mg/mL.	Placebo will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Prefilled syringes will contain the same vehicle and excipients as those for active infusion and injection.
<b>Manufacturer</b>	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380

IMP=investigational medicinal product; iv=intravenous; n/a=not applicable; sc=subcutaneous.

The fremanezumab doses, regimens, and routes of administration to be evaluated in this double-blind, double-dummy, placebo-controlled study were selected on the basis of 3 key factors. First, simulations suggest that maximum observed concentration ( $C_{max}$ ) is the most significant pharmacokinetic parameter in the efficacy of fremanezumab (in migraine). As CH is considered one of the most severe forms of pain a person can experience, treatments that provide quick and lasting relief (ie, for the duration of the cluster period) are a priority for this patient population. Second, the biological nature of the disease mandates the need for any treatment to desensitize the third order neuron, not the second (as is the case in migraine), suggesting that high levels of blockade at the first neuron would be necessary. Third, the favorable safety profile of the drug, as well as clinical and nonclinical safety data on exposure, suggest that the proposed doses, regimens, and routes of administration will not present any safety concerns.

In the current study, high doses are planned for the first dose (900 mg iv or 675 mg sc) in order to provide a rapid response, especially following iv infusion where higher peak plasma  $C_{max}$  generally occurs at or shortly after the end of infusion compared with 5 to 7 days postdose for sc injections. The 2 forms of loading dose will provide data to confirm the benefit of either the iv or sc as loading dose. Monthly doses of fremanezumab at 225 mg sc were added to both the initial dose of 900 mg iv and 675 mg sc for maintenance of efficacy. Based on modelling, the inclusion of a loading dose should allow patients to reach steady state faster. The monthly doses of 225 mg sc in this CCH population will account for the continuous attacks, with less than 1 month free of headaches between attacks, seen with this CH form.

A placebo-controlled design is appropriate given the purpose and objectives of this clinical study. Inclusion of a placebo-control group is consistent with the IHS guidelines for controlled trials of drugs in CH, first edition ([Lipton et al 1995](#)).

**Test IMP:** Fremanezumab

**Reference IMP:** None

**Placebo IMP:** Same vehicle and excipients as those for fremanezumab

**Duration of Patient Participation and Maximal Exposure to IMP:** Patient participation will last for approximately 16 weeks (including a run-in period lasting approximately 4 weeks [+3 days] and a 12-week double-blind treatment period).

**Study Duration:** 24 months from Q4/2016 to Q3/2018

**End of Study:** End of study is defined as the date the last patient attends the EOT/early withdrawal visit.

**Plans for Treatment or Care after the Patient Has Ended Participation in the Study:** Upon completion of the final study assessments, early withdrawal from the study, or discontinuation for any reason, patients will be offered the opportunity to enter a 32-week long-term safety study (as described in Study TV48125-CNS-30058) for safety and ADA evaluation without additional dosing. Patients who satisfactorily complete the study may be offered to enroll the long-term safety Study TV48125-CNC-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In either case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate. A separate protocol was issued for the long-term safety study.

**Inclusion Criteria:** Patients may be included in the study only if they meet all of the following criteria:

- a. Patients are capable of giving signed informed consent as described in [Appendix D](#) which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.
- b. The patient is a man or woman 18 to 70 years of age, inclusive
- c. The patient has history of CCH according to ICHD-3 beta criteria ([Headache Classification Committee of the IHS 2013](#)) for  $\geq 12$  months prior to screening including the following:
  - Attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15 to 180 minutes and occurring from once daily every other day to 8 times a day for more than half of the time when the disorder is active.
  - The pain is associated with at least 1 of the following symptoms or signs: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis and/or ptosis and/or eyelid edema, and/or sense of restlessness or agitation.
  - CH attacks occurring for more than 1 year without remission, or with remission periods lasting less than 1 month.
- d. The patient has a total body weight of  $\geq 45$  kg.
- e. The patient is not using or using  $\leq 2$  concomitant medications that are commonly prescribed as preventive treatments for CH ([Appendix H](#)), regardless of the indication for which the medication was prescribed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.
- f. If a patient is receiving Botox, it should be in a stable dose regimen, considered as having  $\geq 2$  cycles of Botox prior to screening. The patient should not receive Botox during the run-in period up to the evaluation period (12 weeks) where the primary endpoint is evaluated.

- g. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on 85% of days during the run-in period.
- h. The patient has at least 10 CH attacks during the run-in period.
- i. The patient is in good health in the opinion of the investigator as determined by a medical and psychiatric history; medical examination; 12-lead ECG; and serum chemistry, hematology, coagulation, and urinalysis.
- j. Women may be included only if they have a negative serum beta-human chorionic gonadotropin test at screening, are sterile or postmenopausal, and are not lactating. Definitions of sterile and postmenopausal are given in [Appendix E](#).
- k. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 7.5 months after discontinuation of IMP.
- l. Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must agree to use, together with their female partners, acceptable birth control methods for the duration of the study and for 7.5 months after discontinuation of the IMP. Definitions of women of non-childbearing potential, sterile women, and postmenopausal women; male contraception; and highly effective and acceptable birth control methods including examples are given in [Appendix E](#).
- m. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period and to return to the clinic for the follow-up evaluations, as specified in this protocol.

**Exclusion Criteria:** Patients will be excluded from participating in this study if they meet any of the following criteria:

- a. The patient has used systemic steroids for any medical reason (including treatment of the current CH cycle) within  $\leq 7$  days prior to screening.
- b. The patient reports using butalbital on more than 10 days during the 4 weeks prior to screening or using butalbital on more than 10 days during the screening/run-in period.
- c. The patient reports using opioids on more than 15 days during the 4 weeks prior to screening or using opioids on more than 15 days during the screening/run-in period.
- d. The patient has used an intervention/device (eg, scheduled nerve blocks) for headache during the 4 weeks prior to screening.
- e. The patient has clinically significant hematological, renal, endocrine, immunologic, pulmonary, gastrointestinal, genitourinary, cardiovascular, neurologic, hepatic, or ocular disease, at the discretion of the investigator.
- f. The patient has evidence or medical history of clinically significant psychiatric issues determined at the discretion of the investigator.
- g. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.



- h. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], 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.
- i. The patient has a past or current history of cancer or malignant tumor in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.
- j. The patient is pregnant or lactating.
- k. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies.
- l. The patient has participated in a clinical study of a new chemical entity or a prescription medicine within 2 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer.
- m. The patient has participated in a clinical study of a monoclonal antibody within 3 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer, unless it is known that the patient received placebo during the study.
- n. The patient has a history of prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab). If the patient has participated in a clinical study with any of these monoclonal antibodies, it has to be confirmed that the patient received placebo in order to be eligible for this study.
- o. The patient has any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.
- p. The patient has any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation).
- q. The patient has hepatic enzymes (alanine aminotransferase and aspartate aminotransferase)  $>1.5 \times$  the upper limit of normal (ULN) range after confirmation in a repeat test, or the patient has suspected hepatocellular damage that fulfills criteria for Hy's law at screening.
- r. The patient has serum creatinine  $>1.5 \times$  the ULN or evidence of clinically significant renal disease in the judgement of the investigator.
- s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:
  - mentally or legally incapacitated or unable to give consent for any reason
  - in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution
  - unable to be contacted in case of emergency
  - has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

- t. The patient is an employee of the sponsor/participating study center who is directly involved in the study or is the relative of such an employee.
- u. The patient has an active implant for neurostimulation used in the treatment of CH.
- v. The patient is a member of a vulnerable population (eg, people kept in detention).
- w. The patient has a history of alcohol and/or drug abuse that in the investigator’s opinion could interfere with the study evaluations or the patient’s safety.

**Statistical Considerations:**

**Sample Size Rationale:** A sample size of 258 patients (86 evaluable patients completing the study per treatment group) will provide at least 90% power to detect a treatment difference of 4 CH attacks in the monthly average (assuming a common standard deviation [SD] of 8 CH attacks) at a 2-sided alpha level of 0.05. Assuming a 14% discontinuation rate, approximately 300 patients will be randomized in the trial.

**Analysis of Primary Endpoint:** The primary efficacy endpoint for this study will be derived from CH attack data (ie, occurrence and number of CH attacks, duration of CH attack(s), severity of CH attack(s), and acute CH-specific medication and oxygen use) collected daily using an electronic headache diary device.

For the purpose of this study, a CH attack will be endorsed when the following situations occur:

1. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes
2. Either or both of the following:
  - at least 1 of the following symptoms or signs, ipsilateral to the headache:
    - conjunctival injection and/or lacrimation
    - nasal congestion and/or rhinorrhea
    - eyelid edema
    - forehead and facial sweating
    - forehead and facial flushing
    - sensation of fullness in the ear
    - miosis and/or ptosis
  - a sense of restlessness or agitation

**Analysis of Secondary Endpoints:** Secondary efficacy endpoints will be derived from CH attack data (ie, occurrence and number of CH attacks, duration of CH attack(s), severity of CH attack(s), and acute CH-specific medication and oxygen use) collected daily using an electronic headache diary device. In addition, oxygen and acute treatment use will be derived from the concomitant medications inquiries and patient perception of improvement will be evaluated at time points specified in [Table 2](#) using the PPSI.

**Primary Efficacy Analysis:** The primary efficacy endpoint, the mean change from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after

administration of the first dose of the IMP, will be analyzed using an analysis of covariance (ANCOVA). The model will include treatment, baseline number of CH attacks, baseline preventive medication use (yes or no), gender, and region (US or other).

**Sensitivity Analysis:** A sensitivity analysis will be conducted to explore the impact of missing data in the primary efficacy analysis. Details will be provided in the statistical analysis plan.

**Secondary and Exploratory Efficacy Analysis:** The continuous secondary efficacy endpoints will be analyzed using an ANCOVA method or a mixed model for repeated measures. For the proportion of responders, defined as 50% or more reduction from baseline in the monthly average number of CH attacks, data will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no).

**Multiple Comparisons and Multiplicity:** Hochberg's step-up method will be implemented to test primary and secondary endpoints while controlling the overall type 1 error rate at 0.05.

**Safety Analyses:** All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (ie, reasonable possibility, see Section 7.1.4) (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with the test IMP.

Changes in laboratory, ECG, and vital signs measurements data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

Safety data will be summarized descriptively overall and by treatment group. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the clinical study report.

**Tolerability Analysis:** Tolerability was not specifically defined

**Pharmacokinetics Analysis:** Pharmacokinetics plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by treatment group.

In addition, the most appropriate population pharmacokinetics model will be developed, and covariates that may affect it will be tested for inclusion in the model. This analysis will be reported separately.

**Pharmacodynamics Analysis:** Not applicable

**Pharmacokinetics/Pharmacodynamics Analysis:** The pharmacokinetics/pharmacodynamics relationship may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy response(s).

The pharmacokinetics/pharmacodynamics relationship may be estimated using the most appropriate model after comparing different candidate models for their quality of fit. Covariates that may affect the pharmacokinetics/pharmacodynamics relationship will be tested for inclusion in the model. If performed, this analysis will be reported separately.

**Immunogenicity Analysis:** A summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetics profile, IMP efficacy, and clinical safety will be evaluated. This ADA-impact analysis will be reported separately.

**Exploratory Biomarker Analysis:** Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. Analysis will be reported separately. Measurements will be made using validated assays.

**Pharmacogenomic Analysis:** Pharmacogenomic analysis results will be summarized for each gene tested. An attempt will be made to correlate clinical observations (pharmacokinetics, safety, efficacy, or other effects) with the genotypes observed. Additional pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

**Ancillary Studies Analysis:** Analysis will include summary statistics and multimodal algorithms to monitor physiological activity, sleep/wake activity, and treatment responses. Results will be reported separately.

**Planned Interim Analysis:** An interim analysis for futility will be performed once 50% of patients (the first 150 patients) have completed 12-week assessments during the double-blind study period or have withdrawn from the study early. An independent statistician from a third party will perform the analysis.

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## LIST OF ABBREVIATIONS

### List of Abbreviations

Abbreviation	Term
β-HCG	beta-human chorionic gonadotropin
ADA	antidrug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase (SGOT)
AUC	area under the plasma concentration-time curve
AUC <sub>0-∞</sub>	area under the plasma concentration-time curve from time 0 to infinity
CBC	complete blood count
CCH	chronic cluster headache
CDMS	clinical data management system
CFR	Code of Federal Regulations (US)
CGRP	calcitonin gene-related peptide
CH	cluster headache
CL/F	apparent total plasma clearance
CM	chronic migraine
C <sub>max</sub>	maximum observed concentration
CNS	central nervous system
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
ECG	electrocardiography/electrocardiogram
ECH	episodic cluster headache
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EDTA	ethylenediaminetetraacetic acid
EFD	embryo/fetal developmental toxicity
EM	episodic migraine
EOT	end of treatment (visit)
EQ-5D	EuroQol-5 Dimension
EQ-5D-5L	EuroQol-5 Dimension, 5 response level version
FDA	Food and Drug Administration

<b>Abbreviation</b>	<b>Term</b>
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, third revision
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IHS	International Headache Society
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous(ly)
LSO	local safety officer
mAb	monoclonal antibody
PEF	peak expiratory flow
PGIC	Patients’ Global Impression of Change
PPSI	Patient-Perceived Satisfactory Improvement
PRN	as needed
RNA	ribonucleic acid
RSI	reference safety information
sc	subcutaneous(ly)
SD	standard deviation
SF-12	12-Item Short-Form Health Survey
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
$t_{max}$	time to maximum observed concentration
ULN	upper limit of the normal range
$V_z/F$	apparent total volume of distribution during the terminal phase

<b>Abbreviation</b>	<b>Term</b>
WOCBP	women of childbearing potential
WPAI	Work Productivity and Activity Impairment

## 1. INTRODUCTION AND BACKGROUND INFORMATION

### 1.1. Cluster Headache

Cluster headache (CH) is a primary headache disorder characterized by repetitive attacks of excruciating unilateral head pain and associated with cranial autonomic features (such as lacrimation, conjunctival injection, nasal congestion, nasal rhinorrhea, and partial Horner's syndrome) (Rozen 2005). CH attacks last up to 180 minutes and occur from once every other day to 8 times a day. Cluster periods usually last a few months (typically 3 months) followed by remission periods of months to years (Headache Classification Committee of the International Headache Society [IHS] 2013). A unique feature of CH is the circadian and circannual periodicity nature of the headache attacks. Peak time periods for daily CH onset are 0100 to 0200, 1300 to 1500, and after 2100, with night awakening attacks being more severe than those occurring during the day (Rozen 2005). Some patients tend to have seasonal attacks related to the duration of the photoperiod, with the highest incidence of attacks occurring in January or July with possible relation to solstices or equinoxes (Kudrow 1987).

There are 2 forms of CH: episodic cluster headache (ECH), which is the most common form, where distinct pain-free periods lasting at least 1 month are evident, and chronic cluster headache (CCH) occurring for more than 1 year without remission or with remission periods lasting less than 1 month. About 10% to 15% of patients with CH have the CCH form (Headache Classification Committee of the IHS 2013).

The pathophysiology of CH is complex and not fully understood. Current theories implicate mechanisms such as vascular dilation, trigeminal nerve stimulation, and circadian effects. Histamine release, an increase in mast cells, genetic factors, and autonomic nervous system activation may also contribute (Weaver-Agostoni 2013). However, 3 major features of CH are the main focus for understanding its pathophysiological model: trigeminal distribution of the pain (including association with neuropeptide level changes), ipsilateral cranial autonomic features, and (circadian) episodic pattern of attacks (May 2005).

The excruciatingly severe unilateral pain is likely to be mediated by activation of the first (ophthalmic) division of the trigeminal nerve, whereas the autonomic symptoms such as lacrimation are due to activation of the cranial parasympathetic outflow from the seventh cranial nerve (Goadsby 2002). When the trigeminal system becomes highly activated, the excitation spreads to the superior salivary nucleus, resulting in excitation from the sphenopalatine ganglion to parasympathetic nerves of intracranial large blood vessels, lacrimal glands, and nasal mucosa. As a result, ipsilateral autonomic symptoms such as Horner's sign, lacrimation, nasal congestion, and rhinorrhea are manifested (Goadsby 2002, Japanese Headache Society 2013). Stimulation of the superior sagittal sinus activates the trigeminovascular pathway, and this also results in the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) in the external jugular vein. During attacks, the levels of CGRP and VIP are raised in cranial venous blood in all patients.

### **1.1.1. Rationale for Fremanezumab Development as a Preventive Treatment for Cluster Headache**

Worldwide, there are currently no approved medications for the preventive treatment of CH, and medications used off-label in clinical practice for this indication lack meaningful evidence to support their use. Among the medications used for ECH and CCH are short-course corticosteroids for transitional prophylaxis and verapamil (the most common first-line treatment), anti-seizure drugs (valproic acid, topiramate), ergotamine, melatonin, and capsaicin for maintenance prophylaxis. Lithium and deep-brain stimulation have also been used as preventive treatments for CCH ([Weaver-Agostoni 2013](#)). Each of these treatment options is suboptimal due to limited evidence of efficacy, troublesome side effects, and/or an unfavorable risk to benefit ratio ([Rozen 2005](#), [Weaver-Agostoni 2013](#)).

Teva is developing fremanezumab (TEV-48125) for the preventive treatment of CH (chronic and episodic forms). Fremanezumab is a potent, selective CGRP binder and blocks both CGRP isoforms ( $\alpha$ - and  $\beta$ -CGRP) from binding to the CGRP receptor. Fremanezumab is highly specific for CGRP and does not bind to closely related family members amylin, calcitonin, and intermedin. It demonstrates a very weak binding interaction with adrenomedullin ( $>2 \mu\text{M}$  equilibrium dissociation constant). Two mutations were introduced into the constant region of the fremanezumab heavy chain to limit antibody effector functions. This loss of function prevents fremanezumab from stimulating antibody-dependent cell-mediated cytotoxicity and triggering complement-mediated lysis; these activities can lead to unwanted consequences such as cell lysis, opsonization, and cytokine release and inflammation ([Armour et al 1999](#), [Zeller et al 2008](#)).

Similar to migraine, the trigeminal system plays a pivotal role in the pathophysiology of CH. During CH attacks, activation of the trigeminal system causes neurovascular inflammation mediated by CGRP and other neuropeptides ([Fanciullacci et al 1995](#), [Fanciullacci et al 1997](#), [Goadsby and Edvinsson 1994](#)). In CH, the generator appears to be in the posterior grey matter of the hypothalamus (third neuron) ([May et al 1999](#)). Blocking CGRP in the peripheral ganglia of the trigeminal system should result in desensitization of the first and second neurons of the trigeminal system. Fremanezumab does not cross the blood brain barrier, but its demonstrated safety profile (briefly summarized in Section 1.2) provides an opportunity to block the peripheral CGRP released in the trigeminal system, leading to a further desensitization of the third-order neuron in the hypothalamus. Thus, fremanezumab could potentially normalize the system and prevent further attacks without having central nervous system secondary effects.

Few, if any, medical disorders are more painful than CH. Treatments that provide quick and lasting relief (ie, for the duration of the cluster period) and that prevent CH attacks are therefore a priority for this patient population. Results from the Phase 2b studies of fremanezumab in patients with migraine demonstrating onset of efficacy as early as 1 week after treatment and maintenance of effect throughout the 12-week treatment period ([Bigal et al 2015a](#), [Bigal et al 2015b](#)) suggest that fremanezumab may fulfil these treatment needs for patients with CH.

### **1.1.2. Study Purpose**

The purpose of the current study is to evaluate the efficacy and safety of fremanezumab, administered via the intravenous (iv) and/or subcutaneous (sc) routes, in the prevention of CCH in adult patients.



## 1.2. Findings from Nonclinical and Clinical Studies

Brief summaries of nonclinical pharmacology, pharmacokinetics, and toxicology studies and clinical studies are provided in the following sections. More detailed information is provided in the Investigator’s Brochure (IB).

### 1.2.1. Nonclinical Studies

Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP).

In in-vitro studies, fremanezumab demonstrated no potential for Fcγ receptor binding, cytokine release, or hemolysis, up to tested concentrations of 25.5 mg/mL. The concentrations tested in these in vitro assays are relevant to the predicted range of concentrations for administration in human subjects. Fremanezumab prevents in vitro cyclic adenosine monophosphate production induced by CGRP while not binding to similar peptides such as amylin, calcitonin, or adrenomedullin. In vivo pharmacology studies of fremanezumab in animal models indicate that fremanezumab prevented an increase in blood flow in rat paw skin and the middle meningeal artery after electrical stimulation and produced a dose-dependent inhibition of the capsaicin-induced skin flare response in cynomolgus monkey.

Safety pharmacology studies to evaluate potential cardiovascular effect were performed. The data suggest no treatment-related findings after single and repeated administration up to 6 months via once weekly administration at high dose levels (up to 300 mg/kg/week).

Fremanezumab was tested in a series of nonclinical in vivo studies in Sprague Dawley rats and cynomolgus monkeys. Fremanezumab was administered to rats and monkeys by the iv or sc route for up to 3 months in duration and by sc route in the 6-month chronic toxicity study in monkeys, and no toxicological concerns were identified following chronic dosing to experimental animals at dose levels up to 300 mg/kg/week.

It is relevant to note that due to the higher exposure observed in the recent clinical Study TV48125-PK-10078 (Japanese bridging study), a re-evaluation of the safety margins was performed. An internal investigation indicates that the original assay underestimated fremanezumab measured plasma concentrations. Comparison of the exposure parameters of maximum observed concentration ( $C_{max}$ ) and area under the plasma concentration-time curve from time 0 to infinity ( $AUC_{0-\infty}$ ) from Study LBR-101-011 (including iv dosing), which were analyzed by the original bioassay, with the exposure parameters from Study TV48125-PK-10078, which were analyzed using the newer validated assay for the 225- and 900-mg sc dose levels, indicates an apparent exposure difference between 2.9- and 3.5-fold in Study TV48125-PK-10078 relative to Study LBR-101-011. Thus, the most conservative factor of 3.5 was used to recalculate the safety margins, meaning that LBR-101-011 exposure was assumed to be 3.5-fold higher than originally reported and, as such, safety margins decreased by 3.5-fold.

For the 6-month chronic toxicity study in monkeys, the calculated safety margins based on exposure (area under the plasma concentration-time curve [AUC]) at 300 mg/kg/week dose, which was determined as the no observable adverse effect level (NOAEL), is at least 54-fold higher compared to the expected human exposure at a dosing regimen of 900 mg iv loading dose followed by the 225-mg sc monthly dose and at least 20-fold higher relative to  $C_{max}$ .

Nevertheless, it is important to note that the change in safety margins has no impact on the safety profile of fremanezumab based on the overall toxicological data.

In a GLP embryo/fetal developmental toxicity (EFD) study in rabbits, sc injection of fremanezumab to pregnant rabbits was well tolerated and did not induce any obvious maternal toxicity at any dose level. No apparent evidence of embryo-fetal toxicity was noted in any dose group. In addition, a GLP combined fertility and EFD study in rats was conducted, and no treatment-related effects on gonadal function, mating behavior, reproductive performance, and embryo-fetal survival and development were observed in any dose group.

The pharmacokinetics of fremanezumab in animals (rats and monkeys) is typical of a humanized immunoglobulin G2 (IgG2) molecule, with low mean plasma clearance (CL), low volume of distribution at steady state ( $V_{ss}$ ), and a long terminal elimination half-life ( $t_{1/2}$ ). Exposure as defined by  $C_{max}$  and AUC increased linearly across doses following single and repeated once-weekly dosing. No gender differences in exposure were observed in rats or monkeys. Following sc administration, mean systemic exposure values (calculated using AUC from time zero to 168 hours postdose) were 65% to 67% and 81% to 92% of the equivalent iv doses for rats and monkey, respectively, demonstrating reasonably high sc bioavailability.

To conclude, the overall nonclinical safety data presented in this package support the safe, repeated (monthly) administration of fremanezumab in human subjects for the duration of the Phase 3 pivotal trials (3 months) and the long-term safety extension (1 year).

## **1.2.2. Clinical Studies**

The clinical program to date is composed of 6 completed Phase 1 clinical studies in healthy subjects (Studies B0141001, B0141002, B0141006, B0141007, LBR-101-008, and LBR-101-011) and 2 completed Phase 2b clinical studies in patients with migraine (Studies LBR-101-021 and LBR-101-022). In total, 484 subjects/patients (118 healthy subjects and 366 patients with migraine) have received at least 1 dose of fremanezumab via iv or sc routes of administration in these completed studies. In addition, there are 5 ongoing clinical studies of fremanezumab: 2 pivotal efficacy studies in patients with migraine (1 study each for patients with chronic migraine and patients with episodic migraine [Studies TV48125-CNS-30049 and TV48125-CNS-30050]); a long-term safety study in patients with migraine (Study TV48125-CNS-30051); a pharmacokinetic, safety, and tolerability Phase 1 study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078); and a Phase 1 study (Study TV48125-BE-10114) comparing the pharmacokinetics of fremanezumab administered sc using a device referenced to a prefilled syringe configuration.

Further details may be found in the current IB.

### **1.2.2.1. Clinical Pharmacology Studies**

A total of 118 healthy subjects received fremanezumab across 6 completed Phase 1 studies in doses ranging from 0.2 through 2000 mg. Studies included 2 single-ascending-dose pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000

mg administered iv in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study assessing the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011).

These Phase 1 studies were analyzed using the original bioanalytical method that has since been determined to underestimate measured plasma concentrations. In those analyses, fremanezumab pharmacokinetics appeared linear over the dose range from 100 to 2000 mg with  $C_{max}$  and AUC generally increasing in proportion to the dose.

A recently completed pharmacokinetic, safety, and tolerability study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078) dosed fremanezumab as a single sc dose of 225, 675, or 900 mg. Plasma concentration-time profile was measured using the current validated bioanalytical method and the pharmacokinetic results are described below.

The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in  $C_{max}$  and AUC values slightly greater than dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration ( $t_{max}$ ) values generally occurred 5 to 7 days post sc doses. Mean values for apparent total volume of distribution during the terminal phase ( $V_z/F$ ) after a single sc dose ranged from 5.7 to 6.4 L at 225- to 900-mg sc doses. The mean apparent total plasma clearance ( $CL/F$ ) ranged from 0.0777 to 0.0895 mL/min at this dose range. The mean  $t_{1/2}$  ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects. Comparison of exposure parameters ( $C_{max}$  and  $AUC_{0-\infty}$ ) from Studies LBR-101-011 and TV48125-PK-10078 at the 225-mg and 900-mg sc dose levels indicates a 2.9- to 3.5-fold higher exposure in Study TV48125-PK-10078 relative to Study LBR-101-011. The main reason for the difference in exposure appears to be the underestimated concentration values from the original method.

#### 1.2.2.2. Clinical Safety and Efficacy Studies

The safety, tolerability, and efficacy of fremanezumab have been evaluated in 2 completed Phase 2b studies, Studies LBR-101-021 and LBR-101-022, in patients with migraine ([Bigal et al 2015a](#), [Bigal et al 2015b](#)). The results of both studies showed fremanezumab to be superior to placebo for primary and secondary endpoints (benefit at 3 months of therapy).

Fremanezumab was well tolerated with favorable safety profile across the 6 completed Phase 1 and 2 completed Phase 2b studies. In addition, no new safety findings were observed in the ongoing Phase 1 study (Study TV48125-PK-10078), and no serious adverse events considered related to the investigational medicinal product (IMP) have been reported for the ongoing pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125-CNS-30050, as of 23 April 2016). The treatment-emergent adverse events reported in the Phase 1 and Phase 2b studies were predominantly mild to moderate in severity. A specific “pattern of adverse events” that could be associated with a dose or a dose range of fremanezumab, has not been identified; nor has a maximally tolerated dose been identified. Overall, the nature and occurrence of the reported treatment-related adverse events across the clinical program have not raised any specific safety concerns.

No clinically relevant changes in clinical laboratory values, vital signs measurements, or electrocardiogram (ECG) findings have been observed in any of the studies to date.

### **1.3. Known and Potential Benefits and Risks to Patients**

Information regarding the risks and benefits of fremanezumab in patients is summarized in the following sections. Additional information regarding benefits and risks to patients may be found in the IB.

#### **1.3.1. Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)**

Results from Phase 2b clinical studies have demonstrated statistically significant reductions in mean headache hours after 1, 2, and 3 months of sc fremanezumab treatment in patients with chronic migraine and statistically significant reductions in monthly migraine days after 1, 2, and 3 months of fremanezumab treatment in patients with episodic migraine. Results for several secondary/exploratory endpoints also showed fremanezumab to be superior to placebo.

Fremanezumab has generally been well tolerated over the ranges of doses evaluated (single iv infusions at 0.02 to 2000 mg in healthy subjects, multiple iv infusions at 30 to 300 mg in healthy subjects, and multiple sc doses at 225 to 900 mg in healthy subjects and migraine patients). The most common treatment-emergent adverse events across all patients/subjects studied were mild to moderate transient general administration site disorders/reactions. Other commonly reported treatment-emergent adverse events were headache, back pain, and upper respiratory tract infection.

Reports of mild to moderate transient administration site disorders/reactions, including injection site bruising, injection site swelling, administration site pain, injection site pain, injection site pruritus, injection site dermatitis, injection site rash, injection site edema, injection site discomfort, injection site hemorrhage, injection site irritation, injection site mass, and injection site hematoma, have occurred with sc administration. In addition, reports of mild and transient infusion site pain and swelling following iv administration have occurred. Among these events, the following have been identified as adverse drug reactions (identified risks): injection site erythema, administration site pain, injection site pain, injection site pruritus, and injection site dermatitis. None of these identified risks are considered important risks.

Infusion-related reaction and drug hypersensitivity were also identified as adverse drug reactions. To date, 1 subject who received fremanezumab iv had a non-serious infusion-related reaction, and 1 patient who received fremanezumab via the sc route had a non-serious event of drug hypersensitivity. Both events resolved following IMP discontinuation and treatment with diphenhydramine and methylprednisolone. Neither of these identified risks are considered important risks.

Potential risks for TEV-48125 include perivascular inflammation; development of antidrug antibodies (ADAs); liver enzyme elevations; and cardiovascular consequences of CGRP inhibition, including effects on blood pressure, heart rate, or other cardiovascular parameters.

**1.3.2. Overall Benefit and Risk Assessment for This Study**

In summary, the benefit and risk assessment for fremanezumab is favorable following review of the outlined data.

## 2. STUDY OBJECTIVES AND ENDPOINTS

### 2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are as follows:

Objectives	Endpoints
<p>The <b>primary objective</b> of this study is to demonstrate the efficacy of fremanezumab in the prevention of chronic cluster headache (CCH) in adult patients.</p>	<p>The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks during the 12-week period after administration of the first dose of the investigational medicinal product (IMP), ie, based on week 0 to 12 data.</p>
<p>A <b>secondary objective</b> of this study is to further demonstrate the efficacy of fremanezumab in the prevention of CCH in adult patients.</p>	<p>The secondary efficacy endpoints to further demonstrate efficacy are:</p> <ul style="list-style-type: none"> <li>• the proportion of patients with a <math>\geq 50\%</math> reduction from baseline (run-in period) in the monthly average number of CH attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the first dose of the IMP, ie, based on week 0 to 4 data</li> <li>• the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data</li> <li>• the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat CCH during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>• assessment of patient’s perceived improvement, as measured by the Patient-Perceived Satisfactory Improvement (PPSI) at 1, 4, 8, and 12 weeks after</li> </ul>

Objectives	Endpoints
	administration of the first dose of the IMP relative to baseline (day 0)
<p>A <b>secondary objective</b> of this study is to evaluate the safety of fremanezumab in adult patients with CCH.</p>	<p>The secondary safety endpoints are as follows:</p> <ul style="list-style-type: none"> <li>• occurrence of adverse events throughout the study</li> <li>• clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results at each visit</li> <li>• vital signs (systolic and diastolic blood pressure, oral temperature, and pulse rate) measurements at each visit. Note: Oxygen saturation will be measured in cases of suspected anaphylaxis and severe hypersensitivity. Respiratory rate will also be measured in these cases but not as a standard vital sign.</li> <li>• 12-lead electrocardiogram (ECG) findings at screening, baseline, and week 12</li> <li>• use of concomitant medication during the study</li> <li>• clinically significant changes in physical examinations, including body weight</li> <li>• injection site reaction (ie, erythema, induration, and ecchymosis) and injection site pain assessments</li> <li>• occurrence of hypersensitivity/anaphylaxis reactions</li> <li>• suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)</li> </ul>
<p>The <b>immunogenicity objective</b> is to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to iv and sc fremanezumab</p>	<p>The immunogenicity endpoints are ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)</p>

### 2.1.1. Justification of Primary Endpoint

For patients with CCH, headache attacks occur for more than 1 year without remission, or with remission periods lasting less than 1 month (May 2005). The duration of pain in these patients supports the need to evaluate time point of the primary endpoint of 12 weeks. This longer

duration of assessment at 12 weeks in CCH patients should capture the effect on fluctuations in frequency of headaches within the clusters.

## **2.2. Exploratory Objectives and Endpoints**

### **2.2.1. Exploratory Objectives and Endpoints**

The exploratory objectives are as follows:

- to further evaluate the efficacy of fremanezumab in the prevention of CH in adult patients
- to explore the correlation between pharmacokinetic parameters and IMP efficacy
- to explore the relationship between biofluid biomarkers and fremanezumab concentrations
- to explore the relationship between pharmacogenetics versus headache response, CH attack characteristics, and/or safety
- to explore the relationship between soluble exploratory biomarkers versus CH response

The exploratory endpoints are as follows:

- proportion of patients with  $\geq 50\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- proportion of patients with  $\geq 75\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- proportion of patients reaching 100% reduction in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- mean change from baseline (run-in period) in the number of CH attacks during weeks 1, 2, 3, 4, 8, and 12, after administration of the first dose of the IMP
- mean change from baseline (run-in period) in the number of CH attacks during the 8-week period after administration of the first dose of the IMP, ie, based on week 0 to 8 data
- mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the second dose of the IMP, ie, based on week 4 to 8 data
- change from baseline (run-in period) in the severity of CH attacks (mild, moderate, severe, and very severe) during weeks 1, 2, 3, 4, 8, and 12 after administration of the first dose of the IMP



- mean change from baseline (run-in period) in the weekly average number of days with use of any acute headache medications during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- total cumulative distribution of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data
- cumulative distribution function plot of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data
- mean change from baseline (run-in period) in the monthly average number of CH attacks of at least severe severity during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- changes from baseline (day 0) in responses to questionnaires that measure quality of life, satisfaction with treatment, and health status
- the relationship between biofluid biomarkers and fremanezumab concentrations
- the relationship between specific genetic polymorphisms within the calcitonin gene-related peptide (CGRP) receptor-ligand complex and headache-associated genes versus headache response, specific CH attack clinical features (eg, severity, IMP effects, IMP efficacy), and/or safety (eg, adverse events to IMP)
- the relationship between baseline levels and/or mean changes in levels from baseline (day 0) in biofluid biomarkers versus treatment, CH response status (onset/duration), and response status (ie, responders versus nonresponders)

### **2.2.2. Wearable Sensor Substudy Exploratory Objectives and Endpoints**

Wearable sensor substudy exploratory objectives are the following:

- to evaluate changes in sleep-wake parameters during days patients experience CH attacks relative to days free of attacks
- to evaluate changes in sleep-wake parameters in predicting seasonal onset of new CH epoch
- to evaluate changes in attacks during days patients experience CH attacks relative to days free of attacks
- to determine the relationship between attacks and sleep pattern and the frequency of CH attacks
- to determine the relationship between attacks and sleep pattern and the intensity of CH attacks
- to determine the relationship between attacks and sleep pattern and the duration of CH attacks

- to explore the differences in attacks and sleep pattern in patients with CCH
- to examine the relationship between attacks and sleep pattern and that of genetic and biomarker measures
- to evaluate changes in attacks in predicting seasonal onset of new CH episode
- to explore the capability of predicting the onset of a new CH epoch ahead of time

Wearable sensor substudy exploratory endpoints are the following:

- change in total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency on days with and without CH attacks
- the change in the total time of sedentary, light, moderate, and vigorous activity before (6-hour period), during, and after (6-hour period) CH attack relative to days free of attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the frequency of CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache intensity during CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache duration during CH attacks
- the average total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency in patients with CCH
- the correlation between the total time in sedentary, light, moderate and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the genetic and biomarker profiles
- detection of time-dependent patterns composed of lower- and higher-level activity metrics (eg, activity score and sleep/wake patterns)
- cross-correlation between the time-dependent activity patterns and CH attacks
- prediction model for the coming CH attack, intensity, and duration. The input to the prediction model (ie, features) will be selected from the measurements collected by the digital wearable devices, information collected by the self-reporting devices, and aggregated information provided by the calculated endpoints (ie, various statistics)

### **3. STUDY DESIGN**

#### **3.1. General Design and Study Schematic Diagram**

This is a 16-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study to compare the efficacy and safety of 2 dose regimens of fremanezumab versus placebo in adult patients for the prevention of CCH. The study will consist of a screening visit, a run-in period lasting approximately 4 weeks (+3 days), and a 12-week double-blind treatment period. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).

Patients will complete a screening visit (visit 1) after providing written informed consent, and eligible patients will enter a run-in period lasting at least 4 weeks (+3 days) during which they will enter baseline CH attack information into an electronic diary device daily. Patients will return to the study center after completing the run-in period (visit 2 [week 0]). Patients who have at least 10 CH attacks during the run-in period and who continue to meet eligibility criteria (including entry of CH attack information in an electronic diary demonstrating compliance for 85% of days during the run-in period) will be randomly assigned at visit 2 (week 0) in a 1:1:1 ratio to 1 of 3 treatment groups as follows:

- fremanezumab 900-mg iv loading dose group: fremanezumab at 900 mg administered via an approximately 1-hour iv infusion at visit 2 (week 0) followed by fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively)
- fremanezumab 675-mg sc loading dose group: fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) followed by fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively)
- placebo group: placebo administered via an approximately 1-hour iv infusion and as 3 sc injections at visit 2 (week 0) followed by placebo administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively)

In order to maintain blinding throughout the study, the number of infusions and injections at each visit will be the same for all patients regardless of the treatment group to which they are randomized. Thus, all patients will receive an iv infusion of the test IMP or placebo IMP followed by 3 sc injections of the test IMP or placebo IMP at visit 2 (week 0), and all patients will receive single sc injections of the test IMP or placebo IMP at visits 3 and 4 (weeks 4 and 8, respectively).

Randomization will be performed using electronic interactive response technology (IRT). Patients will be randomly assigned with stratification based on sex, country, and baseline concomitant preventive medications (yes/no) to the fremanezumab 900-mg iv loading dose group, the fremanezumab 675-mg sc loading dose group, or the placebo group in a 1:1:1 ratio.

Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit for this study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon

completion of the final study assessments, early withdrawal from the study, or discontinuation for any reason, patients will be offered the opportunity to enter a 32 week long-term safety study (as described in Study TV48125-CNS-30058) for safety and ADA evaluation without additional dosing.

Patients who satisfactorily complete the study may be offered to enroll the long-term safety Study TV48125-CNC-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate. A separate protocol was issued for the long-term safety study.

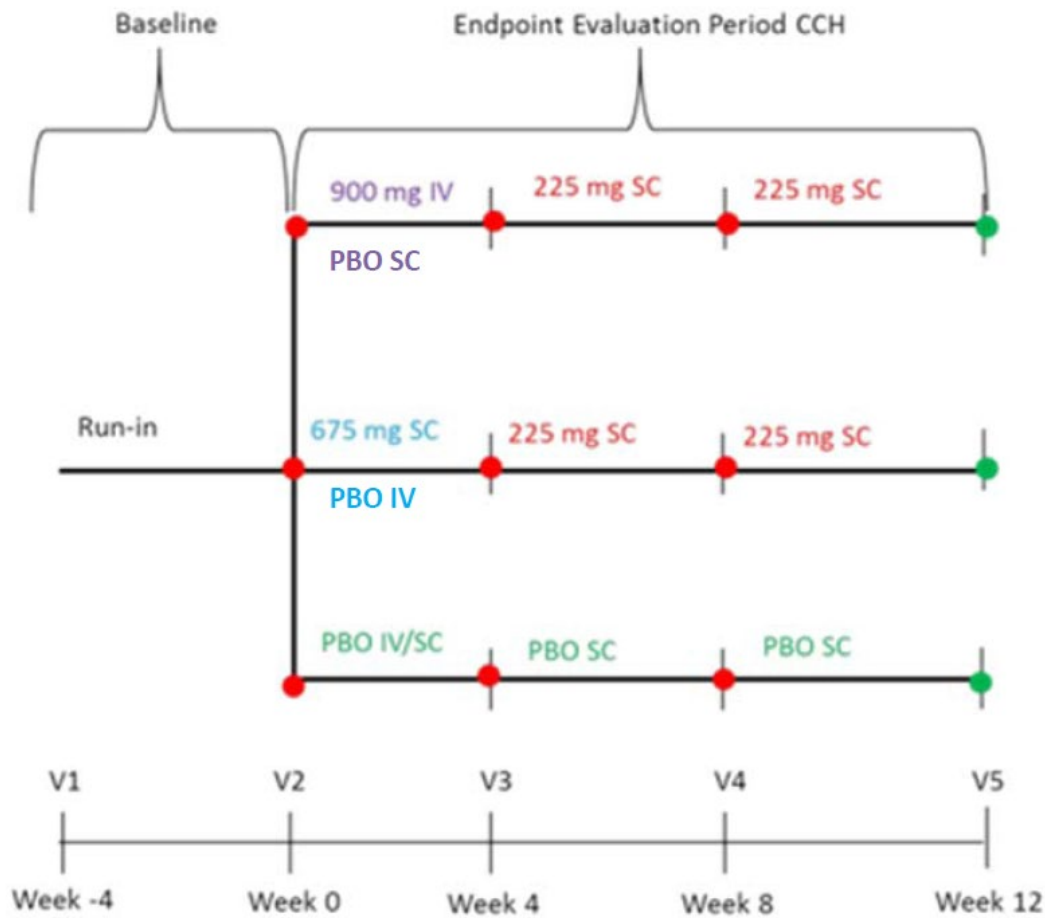
CH attack information will be captured daily during the double-blind treatment period using an electronic diary device. Assessments of change in quality of life and health status (using the Hospital Anxiety and Depression Scale [HADS], EuroQol-5 Dimension [EQ-5D] questionnaire, 12-Item Short-Form Health Survey [SF-12], Impact on Partner and Family questionnaire, and Work Productivity and Activity Impairment [WPAI] questionnaire); satisfaction with treatment (using the PPSI and Patient Global Impression of Change [PGIC] scale); safety evaluations (including eC-SSRS); blood collection for pharmacokinetics, immunogenicity, biomarker, and pharmacogenomics (unless not allowed per local regulation) analyses; and urine sampling for biomarker analysis will be performed at prespecified time points.

The end of study is defined as the last visit of the last patient.

The study duration will be approximately 24 months from Q4/2016 to Q3/2018.

The study schematic diagram is presented in [Figure 1](#).

**Figure 1: Overall Study Schematic Diagram**



CCH=chronic cluster headache; IV=intravenous; PBO=placebo; SC=subcutaneous; V=visit.

Note: Patients randomized to the 900-mg iv loading dose group will receive 900 mg of fremanezumab administered via an approximately 1-hour iv infusion followed by 3 placebo sc injections at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively). Patients randomized to the 675-mg sc loading dose group will receive placebo administered via an approximately 1-hour iv infusion and fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively). Patients randomized to the placebo group will receive placebo as an approximately 1-hour iv infusion followed by placebo administered as 3 placebo sc injections at visit 2 (week 0) and placebo as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively).

**Wearable Sensor Substudy:** A subset of patients in selected investigational sites will be offered the opportunity to participate in a substudy to understand the utility of physiological biomarker measures captured through wearable digital sensor devices as tools to monitor response to treatment and disease symptoms (eg, activity/sleep disruption). Refer to Section 8.6 for additional details.

### 3.2. Planned Number of Patients and Countries

A total of approximately 300 patients (approximately 100 patients per treatment group) are planned to be enrolled in this study. Details on the definition of evaluable patients and sample size are given in Section 9.

The study is planned to be conducted in approximately 12 countries in approximately 80 investigational centers. The study is expected to start in Q4/2016 and last until approximately Q3/2018.

### **3.3. Justification for Study Design and Selection of Population**

The study design follows the recommendations of the IHS guidelines for controlled trials of drugs in CH (Lipton et al 1995), which specify that clinical trials of prophylactic drugs for CH should be parallel-group, placebo-controlled studies in patients meeting the diagnostic criteria set forth by the International Classification of Headache Disorders, third revision beta (ICHD 3-beta) for CCH (Headache Classification Committee of the IHS 2013). Also consistent with the IHS guidelines, patients will be randomized with stratification based on gender (Lipton et al 1995).

The study population will be composed of male and female patients, aged 18 to 70 years, inclusive, with a history of CCH (as defined by ICHD 3-beta criteria [Headache Classification Committee of the IHS 2013]) for at least 12 months prior to screening.

CH is an intensely painful primary headache disorder, and there is a significant unmet medical need for preventive treatments for CH.

### **3.4. Stopping Rules for the Study**

During the conduct of the study, serious adverse events will be reviewed (see Section 7.1.5) as they are reported from the investigational centers to identify safety concerns.

The study may be terminated by the sponsor for any reason at any time. For example, the sponsor should terminate the study in the event the following conditions happen:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- development of the IMP is discontinued
- the interim analysis (performed when 50% of patients have completed 12-week assessments during the double-blind study period or have withdrawn from the study early) supports stopping early for futility

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, consent withdrawn, or adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation as defined in Section 10, noncompliance, or adverse event). In addition, patients with positive eC-SSRS findings or abnormal hepatic laboratory values (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT], bilirubin [total, direct, and indirect], or international normalized ratio [INR]) may meet criteria for discontinuation from the IMP as summarized in Appendix J.

Patients who are discontinued early for any reason will be offered the option to enroll in Study TV48125-CNS-30058 for the purpose of evaluating ADAs and safety (adverse events and concomitant medications).

### **3.5. Schedule of Study Procedures and Assessments**

Study procedures and assessments with their time points are summarized in [Table 2](#). Detailed descriptions of each method of procedures and assessments are provided in [Section 6](#) (efficacy assessments), [Section 7](#) (safety assessments), and [Section 8](#) (pharmacokinetics and other assessments). Study procedures and assessments by visit are listed in [Appendix B](#).

**Table 2: Study Procedures and Assessments**

Study period	Pretreatment period (including screening visit and run-in period)	Double-blind treatment period <sup>a</sup>			
Visit number	V1	V2	V3	V4	V5
Week number	Week -4 - 0	Week 0	Week 4	Week 8	Week 12
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening <sup>b</sup>	Baseline dose 1 day 0 (+3 days)	Visit 3 day 28 (±3 days)	Visit 4 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
Informed consent	X <sup>c</sup>				
Medical and psychiatric history	X				
Prior medication history	X				
Record demographic characteristics	X				
Inclusion and exclusion criteria	X	X			
Randomization		X			
Review study compliance		X	X	X	X
Physical examination, including weight and height <sup>d</sup>	X	X			X
Triplicate 12-lead ECG <sup>e</sup>	X	X			X
Vital signs measurement	X	X	X	X	X
Adverse events <sup>f</sup>	X	X <sup>g</sup>	X	X	X
Concomitant medication inquiry		X	X	X	X
Clinical laboratory tests <sup>h</sup>	X <sup>i</sup>	X	X	X	X
Serum β-HCG test <sup>j</sup>	X				X
Urine β-HCG test		X	X	X	
FSH <sup>k</sup>	X				
Provide electronic diary device <sup>l</sup>	X				



Study period	Pretreatment period (including screening visit and run-in period)	Double-blind treatment period <sup>a</sup>			
Visit number	V1	V2	V3	V4	V5
Week number	Week -4 - 0	Week 0	Week 4	Week 8	Week 12
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening <sup>b</sup>	Baseline dose 1 day 0 (+3 days)	Visit 3 day 28 (±3 days)	Visit 4 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
Enter cluster headache attack information in the electronic diary device <sup>m</sup>	X	X			X
Review electronic diary data		X	X	X	X
Return electronic diary device <sup>n</sup>					X
Blood samples for pharmacokinetics analysis <sup>o</sup>		X	X	X	X
Blood samples for ADA analysis <sup>p</sup>		X	X		X
Blood sample for pharmacogenomic analysis <sup>q</sup>		X			
Blood collection for serum, plasma, and RNA biomarker analysis <sup>f</sup>		X			X
Urine collection for biomarker analysis		X			X
HADS <sup>s</sup>		X	X		X
EQ-5D questionnaire <sup>s</sup>		X	X		X
SF-12 <sup>s</sup>		X	X		X
WPAI questionnaire <sup>s</sup>		X	X		X
Impact on Partner and Family questionnaire <sup>s,t</sup>		X	X		X
PPSI <sup>u</sup>		X	X	X	X
PGIC scale <sup>u</sup>			X	X	X
Provide wearable substudy sensor device and accessories		X			

Study period	Pretreatment period (including screening visit and run-in period)	Double-blind treatment period <sup>a</sup>			
Visit number	V1	V2	V3	V4	V5
Week number	Week -4 - 0	Week 0	Week 4	Week 8	Week 12
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	Screening <sup>b</sup>	Baseline dose 1 day 0 (+3 days)	Visit 3 day 28 (±3 days)	Visit 4 day 56 (±3 days)	EOT or early withdrawal day 84 (±3 days)
Wearable sensor substudy data capture		X <span style="border-top: 1px solid black; display: inline-block; width: 100%;"></span> X			
Wearable sensor device check and compliance check		X	X	X	X
Return wearable sensor device					X <sup>v</sup>
eC-SSRS <sup>w</sup>	X	X	X	X	X
Administration of IMP <sup>x</sup>		X	X	X	
Hypersensitivity/anaphylaxis reaction assessment <sup>y</sup>		X	X	X	
Injection site assessments <sup>z</sup>		X	X	X	

<sup>a</sup> An unscheduled visit may be performed at any time during the study at the patient’s request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

<sup>b</sup> Patients will complete a screening visit and a run-in period lasting at least 4 weeks (+3 days).

<sup>c</sup> The partner or family member who will complete the Impact on Partner and Family questionnaire will be asked to attend the study visit with the patient or to return to the investigational center within ±3 days of the patient’s visit if unable to appear at the same time. Patients involved in the wearable sensor substudy will also provide consent to participate in this substudy.

<sup>d</sup> Height will only be obtained at screening.

<sup>e</sup> ECGs will be performed in triplicate, with approximately 1 to 5 minutes between recordings and will be performed before blood draws and administration of questionnaires.

<sup>f</sup> Adverse events will be recorded from the time informed consent is obtained through the end of study participation.

<sup>g</sup> Inquiries about adverse events will be made before and after IMP administration. Postdose inquiries will be made before the patient leaves the investigational center.

<sup>h</sup> Serum chemistry, hematology, coagulation, and urinalysis. Currently menstruating information (yes, no) will be collected prior to blood and urine collection for laboratory tests for all females.

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- <sup>i</sup> In case of abnormal coagulation during screening (run-in period) or if other specific urgent tests are required, a local retest can be authorized by the sponsor or designee on a case-by-case basis.
- <sup>j</sup> Women of childbearing potential only.
- <sup>k</sup> Postmenopausal women only.
- <sup>l</sup> Eligible patients will be given an electronic diary device and will be trained in its use and compliance requirements on the day of screening.
- <sup>m</sup> Patients will enter CH attack information (ie, occurrence and number of CH attacks, duration of CH attack[s], severity of CH attack[s], and acute CH-specific medication and oxygen use) into the electronic diary device beginning on the day after the screening visit through the EOT/early withdrawal visit.
- <sup>n</sup> Unless the patient begins participation in the long-term safety study (Study TV48125-CNS-30058) on the same day (ie, after completing all assessments/procedures for this visit).
- <sup>o</sup> The blood sample for pharmacokinetics analysis collected at visit 2 (week 0) prior to dosing (from either arm) and at the end of the infusion (+10 minutes) from the arm that is not used for the IMP infusion. All other blood samples for pharmacokinetics analysis will be collected prior to dosing (where applicable) and may be collected from either arm.
- <sup>p</sup> Blood samples for serum ADA assessment (5 mL) will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis. Patients who will not enroll in the double-blind, long-term safety study for treatment, for any reason, will be offered the option to enter the long-term safety study for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) approximately 7.5 months after administration of the last dose of IMP in this study.
- <sup>q</sup> A blood sample for pharmacogenomic analysis will be collected at visit 2 (week 0) or any visit thereafter, unless the patient declines testing or local regulations prohibit testing.
- <sup>r</sup> Blood for further biomarkers analyses will be collected after blood collection for pharmacokinetic and immunogenicity analyses as follows: 8.5 mL for serum, 6 mL for plasma, and 2.5 mL for PAXgene<sup>®</sup> RNA.
- <sup>s</sup> Responses will be recorded in the investigational site tablet.
- <sup>t</sup> Partners/family members will be asked to attend the study visit with the patient or to return to the investigational center within  $\pm 3$  days of the patient's visit if unable to appear at the same time.
- <sup>u</sup> Responses at week 1 will be recorded in the electronic diary device at home, and responses at all other time points will be entered into the investigational site tablet.
- <sup>v</sup> Patients will return the wearable sensor if they do not rollover into the long-term safety study (Study TV-48125-CNS-30058) or if they rollover into the long-term safety study but do not wish to continue participating in the wearable sensor substudy.
- <sup>w</sup> The eC-SSRS Baseline/Screening version will be completed at visit 1, and the eC-SSRS Since Last Visit version will be completed at all other visits, including unscheduled visits. Results from both versions will be entered into the investigational site tablet.
- <sup>x</sup> Patients randomized to the 900-mg iv loading dose group will receive 900 mg of fremanezumab administered via an approximately 1-hour iv infusion followed by 3 placebo sc injections at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively). Patients randomized to the 675 mg sc loading dose group will receive placebo administered via an approximately 1-hour iv infusion followed by fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively). Patients randomized to the placebo group will receive placebo as an approximately 1-hour iv infusion followed by placebo administered as 3 placebo sc injections at visit 2 (week 0) and placebo as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively).
- <sup>y</sup> Patients will be assessed for hypersensitivity reactions and anaphylaxis during and after administration of the IMP (through 1 hour postdose).

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<sup>z</sup> Injection site will be assessed for erythema, induration, ecchymosis, and pain immediately (+10 minutes) and 1 hour (±15 minutes) after IMP administration. If a patient has severe injection site induration, erythema, ecchymosis, or pain at 1 hour after completion of IMP administration, the patient will be reassessed 3 hours (±15 minutes) after completion of IMP administration and hourly (±15 minutes) thereafter until the reaction is of moderate or less severity.

ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin; CH=cluster headache; CRF=case report form; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; EOT=end of treatment; EQ-5D=EuroQol-5 Dimension; FSH=follicle-stimulating hormone; HADS=Hospital Anxiety and Depression Scale; IMP=investigational medicinal product; iv=intravenous; PGIC=Patients' Global Impression of Change; PPSI=Patient-Perceived Satisfactory Improvement; RNA=ribonucleic acid; sc=subcutaneous; SF-12=12-Item Short Form Health Survey; V=visit; WPAI=Work Performance and Activity Impairment.

## 4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be enrolled are not granted by Teva (see [Appendix C](#)). Any deviation from the eligibility criteria will result in study drug discontinuation in the event that a patient has not been dosed.

### 4.1. Patient Inclusion Criteria

Patients may be randomized/enrolled in this study only if they meet all of the following criteria:

- a. Patients are capable of giving signed informed consent as described in [Appendix D](#) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
- b. The patient is a man or woman 18 to 70 years of age, inclusive
- c. The patient has history of CCH according to ICHD-3 beta criteria ([Headache Classification Committee of the IHS 2013](#)) for  $\geq 12$  months prior to screening including the following:
  - Attacks of severe, strictly unilateral pain, which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15 to 180 minutes and occurring from once daily every other day to 8 times a day for more than half of the time when the disorder is active.
  - The pain is associated with at least 1 of the following symptoms or signs: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis and/or ptosis and/or eyelid edema, and/or sense of restlessness or agitation.
  - CH attacks occurring for more than 1 year without remission, or with remission periods lasting less than 1 month.
- d. The patient has a total body weight of  $\geq 45$  kg.
- e. The patient is not using or using  $\leq 2$  concomitant medications that are commonly prescribed as preventive treatments for CH ([Appendix H](#)), regardless of the indication for which the medication was prescribed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.
- f. If a patient is receiving Botox, it should be in a stable dose regimen, considered as having  $\geq 2$  cycles of Botox prior to screening. The patient should not receive Botox during the run-in period up to the evaluation period (12 weeks) where the primary endpoint is evaluated.
- g. The patient demonstrated compliance with the electronic headache diary during the run-in period by entry of headache data on 85% of days during the run-in period.
- h. The patient has at least 10 CH attacks during the run-in period.

- i. The patient is in good health in the opinion of the investigator as determined by a medical and psychiatric history; medical examination; 12-lead ECG; and serum chemistry, hematology, coagulation, and urinalysis.
- j. Women may be included only if they have a negative serum beta-human chorionic gonadotropin ( $\beta$ -HCG) test at screening, are sterile or postmenopausal, and are not lactating. Definitions of sterile and postmenopausal are given in [Appendix E](#).
- k. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 7.5 months after discontinuation of IMP.
- l. Men must be sterile, or if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must agree to use, together with their female partners, acceptable birth control methods for the duration of the study and for 7.5 months after discontinuation of the IMP. Definitions of women of non-childbearing potential, sterile women, and postmenopausal women; male contraception; and highly effective and acceptable birth control methods including examples are given in [Appendix E](#).
- m. The patient must be willing and able to comply with study restrictions, to remain at the clinic for the required duration during the study period and to return to the clinic for the follow-up evaluations, as specified in this protocol.

#### **4.2. Patient Exclusion Criteria**

Patients will not be randomized/enrolled in this study if they meet any of the following criteria:

- a. The patient has used systemic steroids for any medical reason (including treatment of the current CH cycle) within  $\leq 7$  days prior to screening.
- b. The patient reports using butalbital on more than 10 days during the 4 weeks prior to screening or using butalbital on more than 10 days during the screening/run-in period.
- c. The patient reports using opioids on more than 15 days during the 4 weeks prior to screening or using opioids on more than 15 days during the screening/run-in period.
- d. The patient has used an intervention/device (eg, scheduled nerve blocks) for headache during the 4 weeks prior to screening.
- e. The patient has clinically significant hematological, renal, endocrine, immunologic, pulmonary, gastrointestinal, genitourinary, cardiovascular, neurologic, hepatic, or ocular disease, at the discretion of the investigator.
- f. The patient has evidence or medical history of clinically significant psychiatric issues determined at the discretion of the investigator.
- g. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.

- h. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], 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.
- i. The patient has a past or current history of cancer or malignant tumor in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.
- j. The patient is pregnant or lactating.
- k. The patient has a history of hypersensitivity reactions to injected proteins, including monoclonal antibodies.
- l. The patient has participated in a clinical study of a new chemical entity or a prescription medicine within 2 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer.
- m. The patient has participated in a clinical study of a monoclonal antibody within 3 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer, unless it is known that the patient received placebo during the study.
- n. The patient has a history of prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab). If the patient has participated in a clinical study with any of these monoclonal antibodies, it has to be confirmed that the patient received placebo in order to be eligible for this study.
- o. The patient has any finding in the baseline 12-lead ECG considered clinically significant in the judgment of the investigator.
- p. The patient has any finding that, in the judgment of the investigator, is a clinically significant abnormality, including serum chemistry, hematology, coagulation, and urinalysis test values (abnormal tests may be repeated for confirmation).
- q. The patient has hepatic enzymes (ALT and AST)  $>1.5 \times$  the upper limit of normal (ULN) range after confirmation in a repeat test, or the patient has suspected hepatocellular damage that fulfills criteria for Hy's law at screening.
- r. The patient has serum creatinine  $>1.5 \times$  the ULN or evidence of clinically significant renal disease in the judgement of the investigator.
- s. The patient cannot participate or successfully complete the study, in the opinion of their healthcare provider or the investigator, for any of the following reasons:
  - mentally or legally incapacitated or unable to give consent for any reason
  - in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution
  - unable to be contacted in case of emergency
  - has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

- t. The patient is an employee of the sponsor/participating study center who is directly involved in the study or is the relative of such an employee.
- u. The patient has an active implant for neurostimulation used in the treatment of CH.
- v. The patient is a member of a vulnerable population (eg, people kept in detention).
- w. The patient has a history of alcohol and/or drug abuse that in the investigator’s opinion could interfere with the study evaluations or the patient’s safety.

### **4.3. Withdrawal Criteria and Procedures**

Each patient is free to withdraw from the IMP and/or study at any time, without prejudice to their continued care. Patients must be withdrawn from the IMP and/or study if any of the following events occur:

1. Patient withdraws consent or requests discontinuation from the IMP and/or study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.
8. The investigator and/or sponsor may withdraw an individual patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation as defined in Section 10, noncompliance, or adverse event). In addition, patients with positive eC-SSRS findings or abnormal hepatic laboratory values (eg, ALT, AST, ALP, GGT, bilirubin [total, direct, or indirect], or INR) may meet criteria for discontinuation from the IMP as summarized in [Appendix J](#).

In the event that a patient was incorrectly randomized and has already started taking the study drug, a risk/benefit evaluation should take place between the investigator and sponsor and a strong clinical justification must be provided if the patient is not withdrawn from study drug.

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.

Investigators should attempt to obtain information on patients in the case of withdrawal or discontinuation. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal or discontinuation.

See [Appendix F](#) for information regarding how the study will define and address lost to follow-up patients to help limit the amount and impact of missing data.



If a patient is withdrawn from the study for multiple reasons that include also adverse events, the termination page of the CRF should indicate that the withdrawal was related to an adverse event. An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant discontinuation but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be “need to take a prohibited medication” and not the adverse event.

Should a patient decide to withdraw after administration of the IMP or should the investigator decide to withdraw the patient, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made and an explanation given as to why the patient is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF. If a patient withdraws consent, every attempt will be made to determine the reason.

All protocol-specified procedures/assessments should be performed at the early withdrawal visit (see [Appendix B](#)). Patients who withdraw from the study will not be replaced. Patients who withdraw early will be offered the opportunity to enter the long-term safety study (Study TV48125-CNS-30058) for the purpose of evaluation of ADAs and safety (adverse events and concomitant medications) approximately 7.5 months after administration of the last dose of IMP in this study. These patients will not receive any doses of fremanezumab after completing participation in the current study and should be treated with standard of care as appropriate. A patient should only be designated as lost to follow up if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc). In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient’s medical records and transcribed to the CRF.

#### **4.4. Replacement of Patients**

A patient who is randomized/enrolled but does not complete the treatment period will not be replaced with another eligible patient.

#### **4.5. Rescreening**

A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again.

#### **4.6. Screening Failure**

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized/enrolled in the study. Minimal information includes but is not limited to demography, screening failure details, eligibility criteria, and any adverse events or serious adverse events.

## 5. TREATMENTS

### 5.1. Investigational Medicinal Products Used in the Study

IMP is defined as the test IMP and the placebo IMP. Details of the test and placebo IMPs are presented in [Table 3](#).

**Table 3: Investigational Medicinal Products Used in the Study**

IMP Name	Test IMP	Placebo IMP
<b>Trade name and INN, if applicable, or company-assigned number</b>	Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, or RN307])	n/a
<b>Formulation</b>	Solution for injection	Solution for injection
<b>Unit dose strength(s)/Dosage level(s)</b>	225 mg/1.5 mL 900 mg iv loading dose followed by 225 mg sc monthly or 675 mg sc dose followed by 225 mg sc monthly	n/a
<b>Route of administration</b>	Fremanezumab will be administered as iv infusions and sc injections by qualified study personnel at the study center.	Placebo will be administered as iv infusions and sc injections by qualified study personnel at the study center.
<b>Packaging</b>	Fremanezumab will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Prefilled syringes will contain fremanezumab at a concentration of 150 mg/mL.	Placebo will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) on site. Prefilled syringes will contain the same vehicle and excipients as those for active infusion and injection.
<b>Manufacturer</b>	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380

IMP=investigational medicinal product; iv=intravenous; n/a=not applicable; sc=subcutaneous.

Administration of IMP will be via the iv and sc routes. At visit 2, IMP (test or placebo) will be administered via an approximately 1-hour iv infusion followed by 3 sc injections of IMP (test or placebo). At visits 3 and 4, IMP (test or placebo) will be administered as single sc injections. The recommended sc injection sites follow the National Institutes of Health Patient Education Guidelines of September 2015, which are available in [Appendix U](#) of this document and at the following website: [http://www.cc.nih.gov/ccc/patient\\_education/pepubs/subq.pdf](http://www.cc.nih.gov/ccc/patient_education/pepubs/subq.pdf). The suggested sites of injection are back of upper arms, lower abdomen/belly/waistline, and front of thighs. At each visit, the injections should be given in a different location (eg, not in precisely the same place), and study staff member(s) responsible for administration of injections should inspect previous injection sites to ensure that they are free of bruising and tenderness and that proper

rotation of sites is performed. The total number of sc injections and their locations will be recorded for each dosing visit (visits 2 through 4, test or placebo). A 1.5-mL volume from each prefilled syringe must be injected sc for dosing to be considered complete.

### **5.1.1. Test Investigational Medicinal Product**

Fremanezumab is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor. Fremanezumab for CH is being developed for iv and sc administration.

Additional details may be found in [Table 3](#) and in the IB for fremanezumab.

#### **5.1.1.1. Starting Dose and Dose Levels**

Patients randomized to receive fremanezumab will receive either 900 mg or 675 mg. At visit 2 (week 0), iv administration of treatment (IMP or placebo) will precede sc administration (IMP or placebo). Patients randomized to the 900-mg iv loading dose group will receive 900 mg of fremanezumab as an approximately 1-hour iv infusion followed by 3 placebo sc injections at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections (225 mg/1.5 mL) at visits 3 and 4 (weeks 4 and 8, respectively). Patients in the 675-mg sc dose group will receive placebo as an approximately 1-hour iv infusion followed by fremanezumab at 675 mg administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (week 0) and fremanezumab at 225 mg administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively).

#### **5.1.2. Placebo Investigational Medicinal Product**

The placebo will be the same vehicle and excipients as those for fremanezumab. See [Table 3](#) for additional details. Patients randomized to the placebo group will receive placebo administered via an approximately 1-hour iv infusion followed by placebo as 3 sc injections at visit 2 (week 0) and placebo administered as single sc injections at visits 3 and 4 (weeks 4 and 8, respectively).

### **5.2. Preparation, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Products**

Information pertaining to the preparation, handling, labeling, storage, and accountability for the IMP used in this study can be found in [Appendix G](#).

### **5.3. Justification for Investigational Medicinal Products**

#### **5.3.1. Justification for Dose of Test Investigational Medicinal Product**

The fremanezumab doses, regimens, and routes of administration to be evaluated in this double-blind, double-dummy, placebo-controlled study were selected on the basis of 3 key factors. First, simulations suggest that  $C_{max}$  is the most significant pharmacokinetic parameter in the efficacy of fremanezumab (in migraine). As CH is considered one of the most severe forms of pain a person can experience, treatments that provide quick and lasting relief (ie, for the duration of the cluster period) are a priority for this patient population. Second, the biological nature of the disease mandates the need for any treatment to desensitize the third order neuron, not the second (as is the case in migraine), suggesting that high levels of blockade at the first neuron would be necessary. Third, the favorable safety profile of the drug, as well as clinical and

nonclinical safety data on exposure, suggest that the proposed doses, regimens, and routes of administration will not present any safety concerns.

In the current study, high doses are planned for the first dose (900 mg iv or 675 mg sc) in order to provide a rapid response, especially following iv infusion where higher peak plasma  $C_{max}$  generally occurs at or shortly after the end of infusion compared with 5 to 7 days postdose for sc injections. The 2 forms of loading dose will provide data to confirm the benefit of either the iv or sc as loading dose. Monthly doses of fremanezumab at 225 mg sc were added to both the initial dose of 900 mg iv and 675 mg sc for maintenance of efficacy. Based on modelling, the inclusion of a loading dose should allow patients to reach steady state faster. The monthly doses of 225 mg sc in this CCH population will account for the continuous attacks, with less than 1 month free of headaches between attacks, seen with this CH form.

### **5.3.2. Justification for Use of Placebo Investigational Medicinal Product**

A placebo-controlled design is appropriate given the purpose and objectives of this clinical study. Inclusion of a placebo control group is consistent with the IHS guidelines for controlled trials of drugs in CH, first edition ([Lipton et al 1995](#)).

### **5.4. Treatment after the End of the Study**

Patients who successfully complete the final visit of this study may be offered the opportunity to enroll in the long-term safety extension study (Study TV48125-CNS-30058), which includes a treatment period lasting approximately 40 weeks.

Patients who were discontinued early for any reason or who do not enroll in this long-term study for treatment, for any reason, will be offered the option to enter the study for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) at approximately 7.5 months after administration of the last dose of the IMP. These patients will not receive any doses of fremanezumab after completing participation in the current study and should be treated with standard of care as appropriate.

### **5.5. Restrictions**

Patients will be required to comply with the following restrictions:

#### **5.5.1. Activity**

Patients must remain at the investigational site, for safety observation, at least 60 minutes after infusion or according to medical judgment.

#### **5.5.2. Blood Donation**

Patients may not donate blood while taking the IMP and for 5 half-lives (7.5 months) after the last dose of the IMP.

#### **5.5.3. Pregnancy**

Restrictions related to pregnancy and required laboratory values (ie, serum and urine  $\beta$ -HCG tests) are provided in the inclusion and exclusion criteria (Section 4.1 and Section 4.1, respectively). Restrictions in regard to contraception methods are reviewed in [Appendix E](#).

## **5.6. Prior and Concomitant Medication or Treatment**

Any prior or concomitant medication, treatment, or procedure a patient has had 3 months before screening visit (visit 1) and up to the end of study, including follow-up, will be recorded on the CRF. Trade name and INN (if available), indication, dose, and start and end dates of the administered medication will be recorded. The sponsor will encode all medication and treatment according to the World Health Organization (WHO) drug dictionary (WHO Drug).

A maximum of 2 concomitant preventive medications for CCH are allowed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study. A list of permissible preventive medications is provided in [Appendix H](#).

For daily prescribed medications, patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.

All concomitant medications taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medication at each visit.

## **5.7. Procedures for Monitoring Patient Compliance**

The investigator will be responsible for monitoring patient compliance. A check of compliance with IMP intake will be performed during each visit after the IMP has been administered, and IMP accountability records will be completed. If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study. Exposure to IMP will be assessed as required.

## **5.8. Randomization and Blinding**

This is a randomized, double-blind, double-dummy, placebo-controlled study. Patients and investigators will remain blinded to IMP assignment during the study. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active drug and placebo into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and contain prefilled syringes with test IMP or placebo IMP. Adequate kit supply for upcoming study visits will be managed by IRT and kept (refrigerated at 2°C to 8°C) on site.

Patients will be randomly assigned with stratification based on gender, country, and baseline concomitant preventive medication use (yes/no) to the fremanezumab 900-mg iv loading dose group, the fremanezumab 675-mg sc loading dose group, or the placebo group in a 1:1:1 ratio. The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses and interim analyses [by a third-party, unblinded statistician]), and patients will be blinded to treatment assignment throughout the study.

The IRT will manage initial drug supply, maintenance of adequate IMP supplies on site, and study randomization centrally.

## **5.9. Maintenance of Randomization and Blinding**

### **5.9.1. Maintenance of Randomization**

The randomization code will be generated by the IRT third-party vendor, following specifications from the Biostatistics Department. A Teva statistician will be responsible for reviewing the dummy randomization codes, and the final randomization code will be maintained by the third-party vendor in a secure location.

At the time of analysis (after the end of the study), after receiving an unblinding request from the Teva statistician, the service provider will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure (SOP).

### **5.9.2. Blinding and Unblinding**

Blinded pharmacokinetics data may be assessed during the study. Personnel responsible for bioanalysis (pharmacokinetics and immunogenicity) will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetics data analysis will not have access to clinical safety and efficacy data and will provide concentration data to other personnel in a manner that will not identify individual patients (ie, a dummy patient identifier will be linked to the concentration data of an individual patient).

The planned interim analysis (Section 9.15) will be conducted by a third-party, unblinded statistician. Results from the interim analysis will be reported in a manner that does not unblind any blinded individuals (ie, the sponsor, investigators, blinded study staff, and patients).

For information about personnel who may be aware of IMP assignments, see Section 5.8. These individuals will not be involved in conduct of any study procedures or assessment of any adverse events.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the treatment assignment is needed to make treatment decisions, the investigator may unblind the patient's IMP assignment as deemed necessary, mainly in emergency situations, through specialized access in the IRT system. If possible, the sponsor should be notified of the event before breaking of the code. If this is not possible, the sponsor should be notified immediately afterwards, and the patient's randomization code should not be revealed. In emergency cases, breaking of the randomization code can be performed by the investigational center without prior approval by the sponsor.

In the event that the IRT system is not functioning for emergency unblinding, the next course of action is to contact via phone the IRT on-call customer support helpline for manual emergency unblinding.

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded onto the CRF. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the patient's source documentation. Treatment assignment should not be recorded in any study documents or source document.

In blinded studies, for an adverse event defined as a suspected unexpected serious adverse reaction (SUSAR) (ie, reasonable possibility; see Section 7.1.4), Global Patient Safety and

Pharmacovigilance may independently request that the treatment code be broken (on a case-by-case basis) to comply with regulatory requirements. The report will be provided in an unblinded manner for regulatory submission. If this occurs, blinding will be maintained for the investigator and for other personnel involved in the conduct of the study, and analysis and reporting of the data.

### **5.9.3. Data Monitoring Committee**

There will be no Data Monitoring Committee for this study.

### **5.10. Total Blood Volume**

The total blood volume to be collected for each patient enrolling in this study is approximately 131.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed [Appendix J](#).

Details are provided in [Appendix L](#).

## 6. ASSESSMENT OF EFFICACY

Data from any efficacy assessments performed after the specified time will not be collected on the CRF. However, in the event that such data are collected, these data will not be analyzed.

### 6.1. Electronic Diary Device

Efficacy endpoints related to CH attacks will be derived from data collected daily using an electronic diary device. Eligible patients will receive comprehensive training at screening from the investigational site personnel on the use of the electronic diary device. Investigational site personnel will also instruct patients on the requirement for timely and daily completion of the electronic diary.

Patients will complete electronic headache diary entries with questions about the previous day, starting from the day after the screening visit through the end of treatment (EOT)/early withdrawal visit. The electronic headache diary device will allow entry of headache information for up to 2 days after a given day.

Patients who report a CH attack will answer questions about the attack (ie, occurrence and number of CH attacks, duration of CH attack[s], severity of CH attack[s], and acute CH-specific medication and oxygen use). The last day of the run-in period should be reported in the morning of the visit day.

Patients will be asked about their performance at work or at school on CH attack-free days. Additional details can be found in the electronic diary device training manual.

If a patient fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day's information the next time he/she accesses the electronic diary, provided no more than 2 days have elapsed since completion of that day. If more than 2 days have elapsed since completion of a diary day, the patient will not be allowed to enter diary information for that day, and it will be considered a missed day.

If a CH is reported, then CH intensity will be subjectively rated by the patient as follows:

- Mild
- Moderate
- Severe
- Very severe

### 6.2. Hospital Anxiety and Depression Scale

The HADS is a validated and reliable, 14-item scale developed by by [Zigmond and Snaith \(1983\)](#) to measure anxiety (7-items) and depression (7-items). Each item is scored on a 4-point scale from 0 to 3. Scores for depression and anxiety range from 0 to 21; a score of 0 to 7 is normal, 8 to 10 is borderline abnormal, and 11 to 21 is abnormal.

Patients will complete the HADS in the investigational site tablet at the time points detailed in [Table 2](#).



### **6.3. EuroQol-5 Dimension Questionnaire**

The 5 level EQ-5D (EQ-5D-5L) is a standardized questionnaire that assesses overall state of health. The EQ-5D-5L consists of 2 parts. In part 1, patients rate their health state in 5 domains: mobility, self-care, usual activities, pain/discomfort, and mood using a scale of 1 to 5, where 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems. In part 2, patients rate their health state on a 100 mm visual analog scale; a rating of 0 represents the worst imaginable health state, and a rating of 100 represents the best imaginable health state.

Patients will complete the EQ-5D-5L in the investigational site tablet at the time points detailed in [Table 2](#).

### **6.4. Twelve-Item Short-Form Health Survey**

The SF-12 (version 2) is a generic health survey containing 12 questions to measure functional health and well-being rated in 8 health domains (physical function, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) with 1 or 2 questions per domain. The SF-12 was developed from the 36-Item Short-Form Health Survey ([Ware et al 1996](#)). Scores range from 0 to 100, with higher scores indicating better health status.

Patients will complete the SF-12 in the investigational site tablet at the time points detailed in [Table 2](#).

### **6.5. Work Productivity and Activity Impairment Questionnaire**

The generic version of the WPAI questionnaire measures the overall effect of health on productivity at work and daily activities. The specific health problems version of the WPAI questionnaire allows investigators to attribute productivity and activity impairment issues to specific health conditions. After the employment status of a respondent is identified, 3 open-ended questions are asked concerning (1) hours absent from work due to health problems (or specific condition), (2) hours absent from work due to other reasons, and (3) hours actually worked. Two additional questions are included that ask about the impact of health on productivity, 1 concerning productivity at work and the other concerning daily activities outside of work. The response format of each item of the WPAI questionnaire consists of an 11-point scale ranging from 0 (no impairment) to 10 (complete impairment) ([Reilly et al 1993](#)).

Patients will complete the WPAI questionnaire in the investigational site tablet at the time points detailed in [Table 2](#).

### **6.6. Impact on Partner and Family Questionnaire**

The partners/family members of patients participating in the study, if applicable, will complete an Impact on Partner and Family questionnaire at the time points detailed in [Table 2](#). Responses will be recorded in the investigational site tablet. The questionnaire will include questions about the impact of CH on the patient's ability to do chores, the number of days that the patient missed a family or social activity since the last assessment due to CH, and the frequency with which the patient avoids making plans for family/social activities due to CH. Partners/family members will

be asked to attend the study visit with the patient or to return to the investigational center within  $\pm 3$  days of the patient's visit if unable to appear at the same time.

### **6.7. Patient-Perceived Satisfactory Improvement**

The PPSI was developed by [ten Klooster et al \(2006\)](#) for pain intensity and was adjusted for CH symptoms improvement. Patients will mark the level of CH-associated pain and indicate if pain is “much worse,” “moderately worse,” “slightly worse,” “unchanged,” “slightly improved,” “moderately improved,” or “much improved” compared with 4 weeks ago. PPSI will be defined as the change in pain that corresponds with a minimal rating of “slightly improved.”

The PPSI will be completed in the electronic diary device at home at week 1 and in the investigational site tablet at the time points detailed in [Table 2](#).

### **6.8. Patient Global Impression of Change Scale**

The PGIC scale is a validated generic tool for the assessment of overall change in the severity of illness following treatment. Patients will rate the change in their overall health and wellbeing compared with how they felt at the start of the study (the time after the patient received the first IMP dose) as “much worse,” “moderately worse,” “slightly worse,” “stayed the same,” “a little better,” “moderately better,” or “much better.”

Patients will record responses to the PGIC scale in the electronic diary device at home at week 1 and in the investigational site tablet at the time points detailed in [Table 2](#).

## **7. ASSESSMENT OF SAFETY**

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight measurements), injection site reaction/pain assessments, eC-SSRS scores, and use of concomitant medication.

### **7.1. Adverse Events**

#### **7.1.1. Definition of an Adverse Event**

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to fremanezumab. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant.

(Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

Medical occurrences that begin before dosing of the IMP but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF.

### 7.1.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period for this study is defined as the time period from signature of the ICF through the EOT/early withdrawal visit. Adverse events occurring after the EOT/early withdrawal visit for patients who enroll in the long-term safety study (Study TV48125-CNS-30058) will be recorded as part of the long-term safety study database.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed to the CRF, regardless of the severity of the event or judged relationship to the IMP. For serious adverse events and protocol-defined adverse events of special interest (see Section 7.1.7), the serious adverse event form must be completed and the serious adverse event or adverse event of special interest must be reported immediately (see Section 7.1.5.3.1). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events and adverse events of special interest occurring in a patient after the defined study period should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in Section 7.1.5.3.1.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as, “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe”. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the IMP or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding IMP, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed to the CRF.

The relationship of each adverse event to IMP and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

Further details are given in the Safety Monitoring Plan

### 7.1.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the following:

- Mild:** No limitation of usual activities
- Moderate:** Some limitation of usual activities
- Severe:** Inability to carry out usual activities

For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), please refer to Section 7.11.

**7.1.4. Relationship of an Adverse Event to the Test Investigational Medicinal Product**

The relationship of an adverse event to the test IMP is characterized as follows ([Table 4](#)):

**Table 4: The Relationship of an Adverse Event to the Test Investigational Medicinal Product**

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered “no reasonable possibility” if it is clearly due to extraneous causes or if at least 2 of the following apply: <ul style="list-style-type: none"> <li>• It does not follow a reasonable temporal sequence from the administration of the IMP.</li> <li>• It could readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.</li> <li>• It does not follow a known pattern of response to the IMP.</li> <li>• It does not reappear or worsen when the IMP is re-administered.</li> </ul>
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered “reasonable possibility” if at least 2 of the following apply: <ul style="list-style-type: none"> <li>• It follows a reasonable temporal sequence from administration of the IMP.</li> <li>• It cannot be reasonably explained by the known characteristics of the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.</li> <li>• It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists.</li> <li>• It follows a known pattern of response to the IMP.</li> </ul>

**7.1.5. Serious Adverse Events**

For recording of serious adverse events, the study period is defined for each patient as that time period from signature of the ICF to the EOT/early withdrawal visit. Serious adverse events occurring in a patient after the EOT/early withdrawal visit should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in [Section 7.1.5.3.1](#).

**7.1.5.1. Definition of a Serious Adverse Event**

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- results in death

- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.

- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **all** of the below, must be reported by the investigator to the sponsor as a serious adverse event ([Appendix J](#)):

- ALT or AST increase of  $\geq 3 \times$  the ULN
- total bilirubin increase of  $\geq 2 \times$  the ULN
- absence of initial findings of cholestasis (ie, no substantial increase of ALP)
- no other explanation for the observed abnormalities

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

#### **7.1.5.2. Expectedness**

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the IB.

The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.

For the purpose of SUSAR reporting, the version of the IB at the time of occurrence of the SUSAR applies.

### **7.1.5.3. Reporting a Serious Adverse Event**

#### **7.1.5.3.1. Investigator Responsibility**

To satisfy regulatory requirements, all serious adverse events that occur during the study, regardless of judged relationship to administration of the test IMP, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. The investigator does not need to actively monitor patients for adverse events once this study has ended.

Serious adverse events occurring to a patient after the last administration of IMP of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the local safety officer (LSO) or designee (a contract research organization (CRO) in a country without a sponsor LSO) (contact information is in the Clinical Study Personnel Contact Information section); the LSO will forward the report to the sponsor's Global Patient Safety and Pharmacovigilance.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the test IMP (no reasonable possibility, reasonable possibility)

Additional information includes:

- age and sex of patient
- date of first dose of IMP
- date and amount of last administered dose of IMP
- action taken
- outcome, if known
- severity
- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death

- cause of death (whether or not the death was related to IMP)
- autopsy findings (if available)

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the test IMP, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, Independent Ethics Committee/Institutional Review Board (IEC/IRBs), and investigators, according to regulations. The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

For double-blind studies, blinding will be maintained for all study personnel. Therefore, in case of a SUSAR, only the LSO/CRO will receive the unblinded report for regulatory submission; the others will receive a blinded report.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.2).

#### **7.1.5.3.2. Sponsor Responsibility**

If a serious unexpected adverse event is believed to be related to the test IMP or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of fremanezumab and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other action may be required, including the following:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to fremanezumab

#### **7.1.6. Protocol-Defined Adverse Events not for Expedited Reporting**

Not applicable.



### **7.1.7. Protocol-Defined Adverse Events of Special Interest**

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's Global Patient Safety and Pharmacovigilance Department for evaluation: ophthalmic related adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT  $\geq 3 \times$  the ULN, total bilirubin  $\geq 2 \times$  the ULN, or INR  $> 1.5$ ), Hy's Law events, or events of anaphylaxis and severe hypersensitivity reactions. Refer to [Appendix J](#) for guidance regarding monitoring of patients with elevated liver function tests. Anaphylaxis and severe hypersensitivity will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis ([Sampson et al 2006](#)) (also see [Appendix K](#)). In the event of suspected anaphylaxis and severe hypersensitivity, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator. As a precaution, each site should have a resuscitation cart nearby.

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (see Section 7.1.5.3). These events to be reported to the Global Patient Safety and Pharmacovigilance can be either serious or nonserious, according to the criteria outlined in Section 7.1.5.1.

### **7.1.8. Protocol Deviations Because of an Adverse Event**

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be warranted to ensure patient safety. After the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study. The same reporting process as for all other protocol deviations will apply. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient's safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol.

## **7.2. Pregnancy**

Any female subject becoming pregnant during the study will discontinue IMP. All pregnancies of women participating in the study and female partners of men participating in the study, that occur during the study, or within at least 7.5 months after administration of the last dose of the IMP, are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3). The investigator is not required to report female subjects who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

All female subjects or female partners of men participating in the study who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous, elective, or

voluntary abortion). Female partners of men participating in the study who become pregnant will be asked to sign an ICF. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy in the woman participating in the study and/or the female partners of men participating in the study does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

### **7.3. Medication Error and Special Situations Related to the Investigational Medicinal Products**

Any administration of IMP that is not in accordance with the study protocol should be reported as an important deviation, if it meets the important deviation criteria specified in the protocol ([Appendix C](#)), or as a deviation, in the patient’s source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be reported in the clinical trial management system. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety.

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied. Any dose of IMP (whether the test IMP, reference IMP, or placebo IMP), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor. When the identification of the IMP is required, the investigator must follow the procedures for unblinding outlined in [Section 5.9.2](#).
3. Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of IMP which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where an IMP is intentionally used for a medical purpose not in accordance with the authorized product information.

6. Occupational exposure: Exposure to an IMP, as a result of one’s professional or non-professional occupation.
7. Breastfeeding: Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.

#### **7.4. Clinical Laboratory Tests**

All clinical laboratory test results outside of the reference range will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

A laboratory test result that is judged by the investigator as clinically significant will be recorded on the source documentation and the CRF as an adverse event, and monitored as described in Section 7.1.2. An event may include a laboratory or diagnostic test abnormality (once confirmed by repeated testing) that results in the withdrawal of the patient from the study, the temporary or permanent withdrawal of IMP or medical treatment, or further diagnostic work-up. (Note: abnormal laboratory or diagnostic test results at the screening visit that preclude a patient from entering the study or receiving IMP are not considered adverse events.)

In addition, potentially clinically significant values may be predefined by the sponsor for selected laboratory test variables and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan or laboratory analysis plan).

##### **7.4.1. Serum Chemistry, Hematology, and Urinalysis**

Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in [Table 2](#). Clinical laboratory tests will be performed using the central laboratory. However, in case of abnormal coagulation during screening (run-in period) or if other specific urgent tests are required, a local retest can be authorized by the sponsor or designee on a case-by-case basis. Specific laboratory tests to be performed are provided in [Appendix M](#).

##### **7.4.1.1. Human Chorionic Gonadotropin Tests**

A serum  $\beta$ -HCG test will be performed for all WOCBP at screening (visit 1) and EOT (visit 5), and urine  $\beta$ -HCG tests will be performed for WOCBP at all other time points as specified in [Table 2](#). Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

##### **7.4.1.2. Follicle-Stimulating Hormone Tests**

Postmenopausal women will have a follicle-stimulating hormone test at screening (visit 1).

#### **7.5. Physical Examinations**

Physical examinations, including height (to be obtained at the screening visit only) and weight, will be performed at the time points detailed in [Table 2](#). A complete physical examination will include the following organ systems: general appearance; head, eyes, ears, nose, and throat; chest and lungs; heart; abdomen; musculoskeletal; skin; lymph nodes; and neurological. Any physical

examination finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the CRF, and monitored as described in in Section 7.1.2.

## 7.6. Vital Signs

Vital signs (blood pressure [systolic/diastolic], body temperature, and pulse) will be measured before other assessments (eg, blood draws and administration of questionnaires) at the time points detailed in [Table 2](#). All vital signs results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Before pulse and blood pressure are measured, the patient must be in a supine or semi-erect/seated position and resting for at least 5 minutes. The same position and arm should be used each time vital signs are measured for a given patient. For any abnormal vital sign finding, the measurement should be repeated as soon as possible. Any vital sign value that is judged by the investigator as a clinically significant change (worsening) from a baseline value will be considered an adverse event, recorded on the source documentation and transcribed onto the CRF, and monitored as described in Section 7.1.2.

In addition, potentially clinically significant values may be predefined by the sponsor for selected vital signs (see Section 7.6) and, if so, will be documented in the statistical analysis plan or other relevant documents (eg, medical monitoring plan).

## 7.7. Electrocardiography

Twelve-lead ECGs will be conducted before other assessments (eg, blood draws and administration of questionnaires) at the time points detailed in [Table 2](#). The ECGs should be performed after the patient has been supine for at least 5 minutes. The ECGs will be performed in triplicate, with approximately 1 to 5 minutes between recordings.

A qualified physician at a central diagnostic center will be responsible for interpreting the ECG. Electrocardiograms should be performed and transmitted according to the central ECG reading instructions provided in the ECG user manual. Electrocardiogram equipment will be provided to all clinical sites.

Although the ECG interpretation will be performed centrally, the clinical evaluation remains the investigator's responsibility.

The ECG will be evaluated by the investigator at the time of recording (signed and dated), and the printout should be kept in the source documentation file. When potentially clinically significant findings are detected by the investigator, a cardiologist should be consulted for a definitive interpretation. All communications and diagnoses should be filed in the source documentation file. The investigator's interpretation will be recorded in the CRF regardless of the central reading interpretation. Any abnormal findings assessed by the investigator as clinically significant should be recorded in the relevant CRF modules (eg, adverse event, medical history).

Objective alerts are predefined as described in the central ECG reading manual. In these cases, the site and the sponsor will be informed immediately.

Any unscheduled ECGs must also be submitted for central ECG reading.

All ECG results outside of the reference ranges will be judged by the investigator as belonging to one of the following categories:

- abnormal and not clinically significant
- abnormal and clinically significant

Any ECG finding that is judged by the investigator as a potentially clinically significant change (worsening) compared with a baseline value will be considered an adverse event, recorded on the source documentation and in the CRF, and monitored as described in Section 7.1.2.

## **7.8. Immunogenicity**

Blood samples for serum ADA assessment will be collected at the time points detailed in [Table 2](#). Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis. Bioanalytical personnel should be made aware of anaphylaxis occurrence as soon as possible in case an anti-fremanezumab IgE assay is needed. Patients who will not enroll in the double-blind, long-term safety study for any reason will be offered the option to enter the long-term safety study for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) approximately 7.5 months after administration of the last dose of IMP.

Samples from placebo-treated patients will not be analyzed unless the patient elects to enroll into the extension study where the patient will receive fremanezumab treatment. In this case the pre-dose (baseline) sample from the rolled-over placebo patient will be analyzed along with post-treatment samples collected in the extension study and reported in the extension study.

## **7.9. Assessment of Suicidality**

The study population being administered fremanezumab should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing fremanezumab in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with fremanezumab should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

The eC-SSRS will be used to assess the patient's suicidal ideation (severity and intensity) and behavior ([Posner et al 2011](#)). The eC-SSRS Baseline/Screening version will be completed by the patient at visit 1, and the eC-SSRS Since Last Visit version will be completed by the patient at every visit thereafter, including unscheduled visits. Any positive findings on the eC-SSRS Since Last Visit version requires evaluation by a physician or doctoral-level psychologist.

A positive finding will be defined as a current suicide ideation with some intent to act and no plan. The investigator, based on his medical judgment, will determine if the patient should be

seen by a mental health specialist and if he/she should continue participating in the study. If a patient reports current suicide ideation with specific plan and intent, then the patient should be immediately discontinued from the study and seen by a mental health specialist.

Any patient should be excluded if any suicidal behaviors are reported.

Any patient with lifetime behaviors (actual, interrupted, and aborted attempts and preparatory actions) should be excluded and/or discontinued from the study.

### 7.10. Concomitant Therapy or Medication

Concomitant therapy or medication use will be monitored throughout the study. Details of prohibited medications are found in Section 5.6.

### 7.11. Injection Site Assessments

Injection site assessments will be performed immediately (+10 minutes) and 1 hour ( $\pm 15$  minutes) after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, and ecchymosis.

Severity will be graded according to the following criteria:

- Injection site erythema, induration, and ecchymosis will be graded according to measurements: absent, 5 to  $\leq 50$  mm (mild),  $>50$  to  $\leq 100$  mm (moderate), and  $>100$  mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
- For spontaneous report of local pain after the injection, it will be measured as summarized in Table 5.

**Table 5: Severity of Pain Scale for Injection Site Assessments**

Symptom	Severity grade	Assessment
Pain	0	Absent
	1	Mild
	2	Moderate
	3	Severe

If a patient has severe injection site induration, erythema, ecchymosis, or pain at 1 hour after completion of IMP administration, the patient will be reassessed at 3 hours ( $\pm 15$  minutes) after completion of IMP administration and hourly ( $\pm 15$  minutes) thereafter until the reaction is of moderate or less severity.

Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.

Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) should be recorded as adverse events.

## **8. ASSESSMENT OF PHARMACOKINETICS/BIOMARKERS/PHARMACOGENOMIC/IMMUNOGENICITY/ANCILLARY STUDIES**

### **8.1. Pharmacokinetics Assessment**

Sampling for pharmacokinetics will be sparse. Thus, the fremanezumab pharmacokinetics samples will be analyzed using a population pharmacokinetics approach and will be reported separately to the clinical study report.

Blood samples (4 mL) will be collected via venipuncture/indwelling catheter at the time points detailed in [Table 2](#) for plasma concentration measurements of fremanezumab. The dates and times of IMP administration and the date and time of each pharmacokinetics sample will be recorded on the source documentation and transcribed onto the CRF.

Samples from patients who receive active IMP will be analyzed for concentration of fremanezumab using a validated method. Samples from patients who were randomized to receive placebo will not be analyzed. Details on sample handling, storage, shipment, and analysis are given in [Appendix N](#).

### **8.2. Pharmacodynamics Assessment**

Pharmacodynamics parameters are not evaluated in this study.

### **8.3. Immunogenicity Testing**

Blood samples (5 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 2](#) for immunogenicity testing.

Samples from patients who receive active IMP will be analyzed for ADA using a validated method. Samples from patients who receive placebo will not be analyzed unless the patient elects to enroll into an available extension study where the patient will receive fremanezumab treatment. In this case, the pre-dose (baseline) sample from the rolled-over placebo patient will be analyzed along with post-treatment samples collected in the extension study and values will be reported in the extension study. Details on sample handling, storage, shipment, and analysis are provided in [Appendix O](#).

### **8.4. Assessment of Exploratory Biomarkers**

Biomarkers are defined as biological substances that monitor physiological effects, assess drug activity, and predict clinical outcome, safety, and response to therapy. Details on sample handling, storage, shipment, and analysis are provided in [Appendix P](#).

CGRP-containing nerve fibers are prevalent in bone tissue and have been hypothesized to be important in the regulation of bone metabolism, response to bone injury, and the perception of bone pain. In vitro, CGRP is anabolic to osteoblasts and can inhibit maturation to osteoclasts. Preclinical studies suggest CGRP antagonism may have benefit in osteoarthritis ([Benschop et al 2014](#)) and bone-related pain. In the current study, exploratory analysis may be conducted on

blood (serum, plasma, and ribonucleic acid [RNA]) and urine biomarkers for extracellular matrix turnover, bone formation, and bone resorption.

In preclinical models, CGRP can promote angiogenesis in ischemia, capsaicin-induced synovitis, and neovascularization of tumors. Exploratory analysis will be conducted on endothelial/angiogenic markers to determine if fremanezumab alters angiogenic markers.

CGRP is known to act directly on macrophage and dendritic cells by inhibiting them from producing inflammatory cytokines and presenting antigens to T cells. It has been hypothesized that CGRP may act as a regulator of the innate immune response. Exploratory analysis will be conducted on inflammatory endpoints in blood to examine effects of fremanezumab in patients with CH.

Based on the known biology of CGRP's mechanism of action, biomarker assessment will potentially include markers of bone remodeling, inflammation, and angiogenesis. The validated multiplex immunoassay panels will be applied to measure changes in urine, serum, plasma, and RNA biomarkers.

The planned biomarker analysis will be detailed in a separate document, which may be updated at a later stage before the analysis to allow updating with new scientific information.

## **8.5. Pharmacogenomics**

For information regarding pharmacogenomics assessments, see [Appendix Q](#). Multiple genetic loci have been identified that could affect the binding affinity of the CGRP-receptor-ligand complex, while other genetic loci have been identified as having roles in migraine and/or headache onset ([Anttila et al 2013](#)). To explore the potential impact of normal variations in these loci on parameters in this study, a blood sample (6 mL) will be collected from each patient (unless the patient declines testing or local regulations prohibit testing) for pharmacogenomic assessment during this study. Pharmacogenomic assessment potentially includes the association analysis of both known and unknown DNA and RNA genetic variations.

## **8.6. Ancillary Studies – Wearable Sensor Substudy**

At selected sites, a subset of patients (n=45, approximately 15 patients from each treatment group) will be asked to wear a sensor monitoring system (digital wearable device) on the wrist to track sleep patterns and activity patterns. The objective of this substudy is to evaluate changes in sleep-wake parameters and changes in activity as they relate to the occurrence of CH attacks. These changes will be evaluated during days when patients experience CH attacks relative to days free of attacks and will be evaluated for use as predictors of seasonal onset of new CH epoch. The relationship between sleep-wake parameters, activity levels, and the frequency, intensity, and duration of CH attacks will also be determined.

Patients with CH describe their attacks to exhibit remarkable circadian and annual periodicity. The attacks are described to strike at predictable times of the day, mostly related to nocturnal sleep, and the clusters of these at specific times of the year ([Barloese 2012, 2015](#), [Rozen and Fishman 2012](#)). CH attacks are also accompanied by systemic manifestations such as agitation and restlessness ([Barloese 2015](#)).



The data will be used to assess whether changes in patterns of sleep and/or activity as captured by the digital wearable device can be used for early prediction and possible intervention of CH attacks. It is anticipated that risks to patients beyond those listed in Section 1.3 are unlikely.

Patients who are able to demonstrate appropriate use of the wearable device and are willing to comply with the requirements for use of the digital wearable device will be given the device and accessories at the baseline visit. The device will be worn continuously throughout the 12-week treatment period, and for patients who continue into the long-term safety study (Study TV48125-CNS-30058), the device will be worn continuously throughout the 40-week treatment period of that study. Device checks and compliance checks will be done at the study center as described in the schedule of events shown in Table 2. The device will be collected at the time the patient discontinues from the study (ie, at the EOT visit if the patient will not continue participating in the substudy during the long-term safety study or at the early withdrawal visit).

The digital wearable device is provided by Philips and will monitor activity during wake periods, which will be used to quantify relative activity. It will also monitor activity during sleep periods, which will be used to quantify sleep-wake parameters. Data will be obtained with an actigraphy device worn on the wrist. Motion data will be analyzed with either standard analysis techniques and/or advanced signal processing algorithms to extract the maximum amount of information from the data. Further information on the device and its use is provided in the substudy manual.

## **9. STATISTICS**

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the statistical analysis plan. After finalization of the statistical analysis plan, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical study report.

### **9.1. Sample Size and Power Considerations**

A sample size of 258 patients (86 evaluable patients completing the study per treatment group) will provide at least 90% power to detect a treatment difference of 4 CH attacks in the monthly average (assuming a common standard deviation [SD] of 8 CH attacks) at a 2-sided alpha level of 0.05. Assuming a 14% discontinuation rate, approximately 300 patients will be randomized in the trial.

### **9.2. Analysis Sets**

#### **9.2.1. Intent-to-Treat Analysis Set**

The intent-to-treat (ITT) analysis set will include all randomized patients.

In the ITT analysis set, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.

#### **9.2.2. Safety Analysis Set**

The safety analysis set will include all randomized patients who receive at least 1 dose of IMP.

In the safety analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized, unless otherwise specified.

#### **9.2.3. Full Analysis Set**

The full analysis set will include all patients in the ITT analysis set who receive at least 1 dose of IMP and have at least 1 postbaseline efficacy assessment on the primary endpoint.

#### **9.2.4. Per-Protocol Analysis Set**

The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any important protocol deviations. Important protocol deviations will be determined before unblinding/database lock.

In the PP analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized.

### **9.3. Data Handling Conventions**

Efficacy variables from patients who do not have diary entries completed for the entire study period will be imputed. Detailed data imputation rules will be described in the statistical analysis plan.

### **9.3.1. Handling Withdrawals and Missing Data**

Efficacy variables from patients who do not have diary data completed for the entire study period will be imputed. For the analyses based on the proportion of responders, patients who are terminated from the study early will be considered as nonresponders. For patients who complete the study and have intermittent missing days in the e-diary, data will be prorated to 7 days. Details will be provided in the statistical analysis plan.

## **9.4. Study Population**

The ITT analysis set (see Section 9.2.1) will be used for all study population summaries unless otherwise specified. Summaries will be presented by treatment group and for all patients.

### **9.4.1. Patient Disposition**

Data from patients screened; patients screened but not randomized and reason for not randomized; patients who are randomized; patients randomized but not treated; patients in the ITT, safety, and other analysis sets; patients who complete the study; and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

### **9.4.2. Demographic and Baseline Characteristics**

Patient demographic and baseline characteristics, including medical history, prior medications and therapies, and ECG findings will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, SD, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

Treatment groups will be compared for all continuous variables, using an analysis of variance (ANOVA) with treatment group as a factor. The categorical variables of patient sex and race will be summarized using descriptive statistics for each variable category. Missing categories will be presented if necessary. Treatment groups will be compared for all categorical variables using a Pearson's chi-square (or Fisher's exact test if cell sizes are too small).

## **9.5. Efficacy Analysis**

For the purpose of this study, a CH attack will be endorsed when the following situations occur:

1. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes
2. Either or both of the following:
  - at least 1 of the following symptoms or signs, ipsilateral to the headache:
    - conjunctival injection and/or lacrimation
    - nasal congestion and/or rhinorrhea
    - eyelid edema
    - forehead and facial sweating

- forehead and facial flushing
- sensation of fullness in the ear
- miosis and/or ptosis
- a sense of restlessness or agitation

### **9.5.1. Primary Endpoint**

The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data.

### **9.5.2. Secondary Endpoints**

The secondary efficacy endpoints to further demonstrate efficacy are as follows:

- the proportion of patients with a  $\geq 50\%$  reduction from baseline (run-in period) in the monthly average number of CH attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data
- the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the first dose of the IMP, ie, based on week 0 to 4 data
- the mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the third dose of the IMP, ie, based on week 8 to 12 data
- the mean change from baseline (run-in period) in the weekly average number of days with use of cluster-specific acute headache medications (triptans and ergot compounds) during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- the mean change from baseline (run-in period) in the weekly average number of days oxygen is used to treat CCH during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- assessment of patient's perceived improvement, as measured by the PPSI at 1, 4, 8, and 12 weeks after administration of the first dose of the IMP relative to baseline (day 0)

### **9.5.3. Exploratory Endpoints**

The exploratory efficacy endpoints of this study are as follows:

- proportion of patients with  $\geq 50\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- proportion of patients with  $\geq 75\%$  reduction from baseline (run-in period) in the weekly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data

- proportion of patients reaching 100% reduction in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- mean change from baseline (run-in period) in the number of CH attacks during weeks 1, 2, 3, 4, 8, and 12, after administration of the first dose of the IMP
- mean change from baseline (run-in period) in the number of CH attacks during the 8-week period after administration of the first dose of the IMP, ie, based on week 0 to 8 data
- mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the second dose of the IMP, ie, based on week 4 to 8 data
- change from baseline (run-in period) in the severity of CH attacks (mild, moderate, severe, or very severe) during weeks 1, 2, 3, 4, 8, and 12 after administration of the first dose of the IMP
- mean change from baseline (run-in period) in the weekly average number of days with use of any acute headache medications during the 12-week period after administration of the first dose of the IMP, ie, based week 0 to 12 data
- total cumulative distribution of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data
- cumulative distribution function plot of percent reduction ( $\geq 0\%$ ,  $\geq 10\%$ ,  $\geq 20\%$ ,  $\geq 30\%$ ,  $\geq 40\%$ ,  $\geq 50\%$ ,  $\geq 60\%$ ,  $\geq 70\%$ , or  $\geq 80\%$ ) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data
- mean change from baseline (run-in period) in the monthly average number of CH attacks of at least severe severity during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data
- changes from baseline (day 0) in responses to questionnaires that measure quality of life, satisfaction with treatment, and health status
- the relationship between biofluid biomarkers and fremanezumab concentrations
- the relationship between specific genetic polymorphisms within the CGRP receptor-ligand complex and headache-associated genes versus headache response, specific CH attack clinical features (eg. severity, IMP effects, IMP efficacy), and/or safety (eg, adverse events to IMP)
- the relationship between baseline levels and/or mean changes in levels from baseline (day 0) in biofluid biomarkers versus treatment, CH response status (onset/duration), and response status (ie, responders versus nonresponders)

Wearable sensor substudy exploratory endpoints are the following:

- change in total sleep time, sleep onset latency, wake after sleep onset, and sleep efficiency on days with and without CH attacks
- the change in the total time of sedentary, light, moderate, and vigorous activity before (6-hour period), during, and after (6-hour period) CH attack relative to days free of attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the frequency of CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache intensity during CH attacks
- the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache duration during CH attacks
- the average total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency in patients with CCH
- the correlation between the total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the genetic and biomarker profiles
- detection of time-dependent patterns composed of lower- and higher-level activity metrics (eg, activity score and sleep/wake patterns)
- cross-correlation between the time-dependent activity patterns and CH attacks
- prediction model for the coming CH attack, intensity, and duration. The input to the prediction model (ie, features) will be selected from the measurements collected by the digital wearable devices, information collected by the self-reporting devices, and aggregated information provided by the calculated endpoints (ie, various statistics).

#### **9.5.4. Planned Method of Analysis**

The full analysis set (see Section 9.2.3) will be used for all efficacy analyses. Summaries will be presented by treatment group.

##### **9.5.4.1. Primary Efficacy Analysis**

The primary efficacy endpoint, the mean change from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, will be analyzed using an analysis of covariance (ANCOVA). The model will include treatment, baseline number of CH attacks, baseline preventive medication use (yes or no), gender, and region (US or other).

#### **9.5.4.2. Sensitivity Analysis**

Sensitivity analysis may be conducted to explore the impact of missing data in the primary efficacy analysis. Details will be provided in the statistical analysis plan.

#### **9.5.4.3. Secondary and Exploratory Efficacy Analysis**

The continuous endpoints will be analyzed using an ANCOVA or a mixed model for repeated measures. For the proportion of responders, defined as 50% or more reduction from baseline in the monthly average number of CH attacks, data will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no).

### **9.6. Multiple Comparisons and Multiplicity**

Hochberg's step-up method will be implemented to test primary and secondary endpoints while controlling the overall type 1 error rate at 0.05. The treatment comparisons will be for the fremanezumab 900-mg iv loading dose group versus placebo [ $H_{01}$ ] and the fremanezumab 675-mg sc loading dose group versus placebo [ $H_{02}$ ]. According to Hochberg step-up method, the rules of multiple comparisons for 2 null hypotheses for the primary endpoint are as follows:

1. If the resulting 2-sided p-values from both comparisons are  $\leq 0.05$  (reject both null hypotheses), then the next comparison of interest will be interpreted inferentially at the alpha level of 0.05 and statistical significance will be claimed for both active dose groups. Testing of secondary efficacy measures will be continued.
2. If the resulting 2-sided p-value from 1 of comparisons is  $> 0.05$  (fail to reject the null hypothesis) and the other resulting 2-sided p-value is  $\leq 0.025$  ( $\alpha/2=0.025$ ; reject the null hypothesis), the result from the comparison with p-value  $\leq 0.025$  will be interpreted inferentially at the alpha level of 0.05, and statistical significance will be claimed for this active dose group. No other comparison(s) will be interpreted inferentially.
3. If the resulting 2-sided p-value from both comparisons are  $> 0.05$  (fail to reject both null hypotheses), no statistical significant will be claimed and no comparisons will be interpreted inferentially.

If the resulting 2-sided p-values from both comparisons for the primary endpoint are  $\leq 0.05$  (reject both hypotheses; case 1 as described above), testing of secondary efficacy measures will proceed at an error rate of 0.05 in the sequential manner as specified in Section 2.1. The same testing rules as described above will be followed. This process will continue either until all comparisons of interest for secondary endpoints are interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest is  $> 0.05$ . At the point where a 2-sided p-value is  $> 0.05$ , the testing process stops. No further comparisons will be interpreted inferentially.

### **9.7. Safety Analysis**

Safety analyses will be performed on the safety analysis set (Section 9.2.2). Safety assessments and time points are provided in Table 2.

All adverse events will be coded using the Medical Dictionary for Regulatory Activities. Each patient will be counted only once in each preferred term or system organ class category for the

analyses of safety. Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to test IMP (defined as related or with missing relationship) (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Patient listings of serious adverse events and adverse events leading to withdrawal will be presented.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the patient is treated with IMP.

Changes in laboratory, ECG, and vital signs measurement data will be summarized descriptively. All values will be compared with prespecified boundaries to identify potentially clinically significant changes or values, and such values will be listed.

Safety data will be summarized descriptively overall and by treatment group. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, patient counts and percentages will be provided. Descriptive summaries of serious adverse events, patient withdrawals due to adverse events, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any patient dies during the study, a listing of deaths will be provided, and all relevant information will be discussed in the patient narrative included in the clinical study report.

## **9.8. Tolerability Analysis**

Tolerability was not specifically defined.

## **9.9. Pharmacokinetics Analysis**

Pharmacokinetics plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by treatment group.

In addition, the most appropriate population pharmacokinetics model will be developed, and covariates that may affect it will be tested for inclusion in the model. This analysis will be reported separately.

## **9.10. Pharmacokinetic/Pharmacodynamics Analysis**

The pharmacokinetics/pharmacodynamics relationship may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy response(s).

The pharmacokinetics/pharmacodynamics relationship may be estimated using the most appropriate model after comparing different candidate models for their quality of fit. Covariates that may affect the pharmacokinetics/pharmacodynamics relationship will be tested for inclusion in the model. If performed, this analysis will be reported separately.



**9.11. Pharmacogenomic Analysis**

Pharmacogenomic analysis results will be summarized for each gene tested. An attempt will be made to correlate clinical observations (pharmacokinetics, safety, efficacy, or other effects) with the genotypes observed. Additional pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

**9.12. Biomarker Analysis**

Biomarker analysis will include logistic regression, receiver operating characteristic curves, and summary statistics. Results will be reported separately. Measurements will be made using validated assays.

**9.13. Immunogenicity Analysis**

A summary of immunogenicity results will be provided, and the incidence of immunogenicity will be calculated. The impact of immunogenicity on the pharmacokinetics profile, IMP efficacy, and clinical safety will be evaluated. This ADA impact analysis will be reported separately.

**9.14. Ancillary Study Analysis**

Analysis will include summary statistics and multimodal algorithms to monitor physiological activity, sleep/wake activity, and treatment responses. Results will be reported separately.

**9.15. Planned Interim Analysis**

An interim analysis for futility will be performed once 50% of patients (the first 150 patients) have completed 12-week assessments during the double-blind study period or have withdrawn from the study early. An independent statistician from a third party will perform evaluations.

**9.16. Reporting Deviations from the Statistical Plan**

Deviations from the statistical plan, along with the reasons for the deviations, will be described in protocol amendments, the statistical analysis plan, the clinical study report, or any combination of these, as appropriate, and in accordance with applicable national, local, and regional requirements and regulations.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

Refer to [Appendix C](#) for information regarding quality control and quality assurance. This includes information about protocol amendments, deviations, and responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.

Refer to [Appendix R](#) for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

## **11. COMPLIANCE STATEMENT**

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use). Any episode of noncompliance will be documented.

The investigator is responsible for performing the clinical study in accordance with this protocol and the applicable GCP guidelines referenced above for collecting, recording, and reporting the data accurately and properly. Agreement of the investigator to conduct and administer this clinical study in accordance with the protocol will be documented in separate clinical study agreements with the sponsor and other forms as required by national competent authorities in the country where each investigational center is located.

The investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the clinical study; and must ensure that trained personnel are immediately available in the event of a medical emergency. The investigator and the involved clinical study personnel must be familiar with the background and requirements of the study; and with the properties of the IMPs as described in the IB or prescribing information.

The principal investigator at each investigational center has the overall responsibility for the conduct and administration of the clinical study at that investigational center and for contacts with study management, with the IEC/IRB, and with competent authorities.

See [Appendix D](#) for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

## **12. DATA MANAGEMENT AND RECORD KEEPING**

See [Appendix S](#) for information regarding data management and record keeping. This includes direct access to source data and documents, data collection, data quality control, and archiving of CRFs and source documents.

### **13. FINANCING AND INSURANCE**

A separate clinical study agreement, including a study budget, will be signed between each principal investigator and the sponsor (or the CRO designated by the sponsor) before the IMP is delivered.

The patients in this clinical study are insured in accordance with applicable legal provisions. The policy coverage is subject to the full policy terms, conditions, extensions, and exclusions. Excluded from the insurance coverage are inter alia, damages to health, and worsening of previous existing disease that would have occurred or continued if the patient had not taken part in the clinical study.

The policy of Clinical Trials Insurance will be provided to the investigational centers by the sponsor.

For covered clinical studies (see 21CFR54), the investigator will provide the sponsor with financial information required to complete Food and Drug Administration (FDA) 3454 form. Each investigator will notify the sponsor of any relevant changes during the conduct of the study and for 1 year after the study has been completed.

#### **14. PUBLICATION POLICY**

See [Appendix T](#) for information regarding the publication policy.

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## **16. SUMMARY OF CHANGES TO THE PROTOCOL**

### **16.1. Amendment 02 Dated 01 May 2017**

The primary reason for this amendment is to provide clarification based on feedback from participating investigators and regulatory agencies. This amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative.

These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients or the scientific value of the clinical study.

[Table 2](#) (Study Procedures and Assessments) has been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/justification for change
<b>Section 1.2.1, Nonclinical Studies</b>		
Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP) <del>via the iv and sc routes of administration with once weekly dosing for up to 6 months.</del>	Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP).	Revised for clarification.
<u>It is relevant to note that due to the higher exposure observed in the recent clinical Study TV48125-PK-10078 (Japanese bridging study), a re-evaluation of the safety margins was performed. An internal investigation indicates that the original assay underestimated fremanezumab measured plasma concentrations. Comparison of the exposure parameters of maximum observed concentration (C<sub>max</sub>) and area under the plasma concentration-time curve from time 0 to infinity (AUC<sub>0-∞</sub>) from Study LBR-101-011 (including iv dosing), which were analyzed by the original bioassay, with the exposure parameters from Study TV48125-PK-10078, which were analyzed using the newer validated assay for the 225-mg and 900-mg sc dose levels, indicates an apparent exposure difference between 2.9- and 3.5-fold in Study TV48125-PK-10078 relative to Study LBR-101-011. Thus, the most conservative factor value of 3.5 was used to recalculate the safety margins, meaning that LBR-101-011 exposure was assumed to be 3.5-fold higher than originally reported, and as such, safety margins decreased by 3.5-fold.</u>	It is relevant to note that due to the higher exposure observed in the recent clinical Study TV48125-PK-10078 (Japanese bridging study), a re-evaluation of the safety margins was performed. An internal investigation indicates that the original assay underestimated fremanezumab measured plasma concentrations. Comparison of the exposure parameters of maximum observed concentration (C <sub>max</sub> ) and area under the plasma concentration-time curve from time 0 to infinity (AUC <sub>0-∞</sub> ) from Study LBR-101-011 (including iv dosing), which were analyzed by the original bioassay, with the exposure parameters from Study TV48125-PK-10078, which were analyzed using the newer validated assay for the 225-mg and 900-mg sc dose levels, indicates an apparent exposure difference between 2.9- and 3.5-fold in Study TV48125-PK-10078 relative to Study LBR-101-011. Thus, the most conservative factor of 3.5 was used to recalculate the safety margins, meaning that LBR-101-011 exposure was assumed to be 3.5-fold higher than originally reported, and as such, safety margins decreased by 3.5-fold.	Added updated information for nonclinical studies.
For the 6-month chronic toxicity study in monkeys, the calculated safety margins based on exposure (area under the plasma concentration-time curve [AUC]) at 300 mg/kg/week dose, which was determined as the no observable adverse effect level (NOAEL), is at least <del>150</del> 54-fold higher compared to the expected <u>human</u> exposure at a dosing regimen of 900 mg iv loading dose followed by the 225 mg sc monthly dose and at least 20-fold higher relative to C <sub>max</sub> .	For the 6-month chronic toxicity study in monkeys, the calculated safety margins based on exposure (area under the plasma concentration-time curve [AUC]) at 300 mg/kg/week dose, which was determined as the no observable adverse effect level (NOAEL), is at least 54-fold higher compared to the expected human exposure at a dosing regimen of 900 mg iv loading dose followed by the 225 mg sc monthly dose and at least 20-fold higher	Added updated information for nonclinical studies.

Original text with changes shown	New wording	Reason/justification for change
<p>Nevertheless, it is important to note that the change in safety margins has no impact on the safety profile of fremanezumab based on the overall toxicological data.</p>	<p>relative to <math>C_{max}</math>. Nevertheless, it is important to note that the change in safety margins has no impact on the safety profile of fremanezumab based on the overall toxicological data.</p>	
<p><b>Section 1.2.2, Clinical Studies</b></p>		
<p>In addition, there are <u>5</u> ongoing clinical studies of fremanezumab: 2 pivotal efficacy studies in patients with migraine (1 study each for patients with chronic migraine and patients with episodic migraine [Studies TV48125-CNS-30049 and TV48125-CNS-30050]); a long-term safety study in patients with migraine (Study TV48125-CNS-30051); <del>and</del> a pharmacokinetic, safety, and tolerability <u>Phase 1</u> study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078); <del>and a Phase 1 study (Study TV48125-BE-10114) comparing the pharmacokinetics of fremanezumab administered sc using a device referenced to a prefilled syringe configuration.)</del>.</p>	<p>In addition, there are 5 ongoing clinical studies of fremanezumab: 2 pivotal efficacy studies in patients with migraine (1 study each for patients with chronic migraine and patients with episodic migraine [Studies TV48125-CNS-30049 and TV48125-CNS-30050]); a long-term safety study in patients with migraine (Study TV48125-CNS-30051); a pharmacokinetic, safety, and tolerability Phase 1 study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078); and a Phase 1 study (Study TV48125-BE-10114) comparing the pharmacokinetics of fremanezumab administered sc using a device referenced to a prefilled syringe configuration.</p>	<p>Added updated information for clinical studies.</p>
<p><b>Section 1.2.2.1, Clinical Pharmacology Studies</b></p>		
<p>A total of 118 healthy subjects received fremanezumab across 6 completed Phase 1 studies in doses ranging from 0.2 through 2000 mg. <del>Studies Completed studies</del> included 2 single-ascending-dose pharmacokinetics and pharmacodynamics studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects <u>of</u> administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered <u>iv</u> in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study <del>assessing</del> <u>comparing</u> the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011).</p>	<p>A total of 118 healthy subjects received fremanezumab across 6 completed Phase 1 studies in doses ranging from 0.2 through 2000 mg. Studies included 2 single-ascending-dose pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered iv in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study assessing the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy</p>	<p>Added updated information for pharmacology studies.</p>

Original text with changes shown	New wording	Reason/justification for change
<p><u>These Phase 1 studies were analyzed using the original bioanalytical method that has since been determined to underestimate measured plasma concentrations compared with the current validated assay. In those analyses, fremanezumab pharmacokinetics. The pharmacokinetics (noncompartmental analysis) of fremanezumab appeared linear over the dose range from 100 to 2000 mg, with C<sub>max</sub> and AUC parameters generally increasing in proportion to the dose. A recently completed pharmacokinetic, safety, and tolerability study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078) dosed fremanezumab as a single sc dose of 225, 675, or 900 mg. Plasma concentration-time profile was measured using the current validated bioanalytical method, and the pharmacokinetic results are described below. The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C<sub>max</sub> and AUC values slightly greater than dose proportionality over the sc dose range of 225 to 900 mg. Median time to</u> <del>At lower doses (1 to 30 mg), exposure was lower than expected based upon the proportional pharmacokinetics observed at higher doses. C<sub>max</sub> generally occurred at or shortly after the end of infusion, with median time of maximum observed concentration (t<sub>max</sub>) values was generally of 1.0 to 5 to 7 days post sc doses. 0 hours postdose after a 1 hour infusion. However, absorption was prolonged following sc administration, as indicated by the delayed C<sub>max</sub> (median t<sub>max</sub> of 96 to 108 hours postdose). Mean values for apparent total volume of distribution during the terminal phase (V<sub>z</sub>/F) the V<sub>ss</sub> after a single sc iv dose ranged from 5.7 to 6.49 to 13 L at 225- to 900-mg sc doses of 30 to 2000 mg. The mean apparent total plasma clearance (CL/F) ranged from 0.0777 to 0.0895 mL/min 276 L/day at this dose range. The mean t<sub>1/2</sub> ranged from 32.2 to 53.4 days within the dose range of 30 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were</del></p>	<p>subjects (Study LBR-101-011). These Phase 1 studies were analyzed using the original bioanalytical method that has since been determined to underestimate measured plasma concentrations. In those analyses, fremanezumab pharmacokinetics appeared linear over the dose range from 100 to 2000 mg with C<sub>max</sub> and AUC generally increasing in proportion to the dose. A recently completed pharmacokinetic, safety, and tolerability study in healthy Japanese and Caucasian subjects (Study TV48125-PK-10078) dosed fremanezumab as a single sc dose of 225, 675, or 900 mg. Plasma concentration-time profile was measured using the current validated bioanalytical method, and the pharmacokinetic results are described below. The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C<sub>max</sub> and AUC values slightly greater than dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t<sub>max</sub>) values was generally 5 to 7 days post sc doses. Mean values for apparent total volume of distribution during the terminal phase (V<sub>z</sub>/F) after a single sc dose ranged from 5.7 to 6.4 L at 225- to 900-mg sc doses. The mean apparent total plasma clearance (CL/F) ranged from 0.0777 to 0.0895 mL/min at this dose range. The mean t<sub>1/2</sub> ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects. Comparison of exposure parameters (C<sub>max</sub> and AUC<sub>0-∞</sub>) from Studies LBR-101-011 and TV48125-PK-10078 at the 225- and 900-mg sc dose levels indicates a 2.9- to 3.5-fold higher exposure in Study TV48125-PK-10078 relative to Study LBR-101-011. The main reason for the difference in exposure appears to be the bioanalytical method used in the plasma</p>	

Original text with changes shown	New wording	Reason/justification for change
<p>2000 mg. Absolute bioavailability of the sc dose was similar for <u>healthy Japanese and Caucasian subjects. Comparison of exposure parameters (<math>C_{max}</math> and <math>AUC_{0-\infty}</math>)</u><del>the 2 different doses (225 and 900 mg) and ranged from Studies LBR-101-011 and TV48125-PK-10078 at the 225- and 900-mg sc dose levels indicate a 2.9- approximately 54% to 56% for the 225 and 900 mg to 3.5-fold higher exposure in Study TV48125-PK-10078 relative to Study LBR-101-011. The main reason for the difference in exposure appears to be the underestimated concentration values from the original method</del><u>doses, respectively.</u></p>	<p>sample analysis.</p>	
<p><b>Section 1.2.2.2, Clinical Safety and Efficacy Studies</b></p>		
<p>Fremanezumab was well tolerated with favorable safety profile across the 6 completed Phase 1 and 2 completed Phase 2b studies. In addition, no new safety findings were observed in <del>the first cohort of 12 Japanese subjects from the ongoing Phase 1 study (Study TV48125 PK 10078), and no serious adverse events considered related to the investigational medicinal product (IMP) have been reported for the ongoing pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125 CNS-30050, as of 23 April 2016).</del></p>	<p>Fremanezumab was well tolerated with favorable safety profile across the 6 completed Phase 1 and 2 completed Phase 2b studies. In addition, no new safety findings were observed in <del>the first cohort of 12 Japanese subjects from the ongoing Phase 1 study (Study TV48125 PK 10078), and no serious adverse events considered related to the investigational medicinal product (IMP) have been reported for the ongoing pivotal efficacy studies (Studies TV48125-CNS-30049 and TV48125 CNS-30050, as of 23 April 2016).</del></p>	<p>Updated for clarification.</p>
<p><b>Section 2.2.1, Exploratory Objectives and Endpoints (other section affected by this change: Section 3.1 Study Design, Section 9.5.3, Exploratory Endpoints)</b></p>		
<ul style="list-style-type: none"> <li>changes from baseline (day 0) in responses to questionnaires that measure quality of life, <u>satisfaction with treatment, and</u><del>health status, and CH-associated disability</del></li> </ul>	<ul style="list-style-type: none"> <li>changes from baseline (day 0) in responses to questionnaires that measure quality of life, satisfaction with treatment, and health status</li> </ul>	<p>Edited exploratory objective for clarity.</p>
<p><b>Section 3.1, General Design and Study Schematic Diagram (other sections affected by this change: Section 3.4, Stopping Rules for the Study; Section 3.5, Table 2: Schedule of Study Procedures and Assessments [footnote p]; Section 4.3, Withdrawal Criteria and Procedures; Section 5.4, Treatment after the End of the Study; and Section 7.8, Immunogenicity)</b></p>		
<p>Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit for this</p>	<p>Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit</p>	<p>Added clarification that all patients will be offered</p>

Original text with changes shown	New wording	Reason/justification for change
<p>study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon <del>satisfactory</del> completion of the final study assessments, <u>early withdrawal from the study or discontinuation for any reason</u>, patients <del>will</del><u>may</u> be offered the opportunity to enter a <del>32 68</del>-week long-term safety study (as <del>described in</del> Study TV48125-CNS-30058) <del>for safety</del>; <del>consisting of a 40-week long-term treatment period and ADA evaluation without additional dosing, a final follow-up visit approximately 7.5 months after the last dose of the IMP. A separate protocol will be issued for the long-term safety study. Patients who do not enroll in the long-term safety study for any reason may be offered the opportunity to enter the study for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) at approximately 7.5 months after receiving the last dose of the IMP.</del></p> <p><u>Patients who satisfactorily complete the study may be offered to enroll the long-term safety study TV48125-CNC-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate. A separate protocol was issued for the long-term safety study.</u></p> <p>CH attack information will be captured daily during the double-blind treatment period using an electronic diary device. Assessments of <del>CH-related disability</del>, change in quality of life, and health status (using the Hospital Anxiety and Depression Scale [HADS], EuroQol-5 Dimension [EQ-5D] questionnaire, 12-Item Short Form Health Survey [SF-12], Impact on Partner and Family questionnaire, and Work Productivity and Activity Impairment [WPAI] questionnaire); satisfaction with treatment (using the PPSI and Patients’ Global Impression of Change</p>	<p>for this study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon completion of the final study assessments, early withdrawal from the study or discontinuation for any reason, patients will be offered the opportunity to enter a 32 week long-term safety study (as described in Study TV48125-CNS-30058) for safety and ADA evaluation without additional dosing.</p> <p>Patients who satisfactorily complete the study may be offered to enroll the long-term safety study TV48125-CNC-30058 for 68 weeks (as described in this study protocol) to receive additional dosing and a final follow-up visit for safety and ADA evaluation. In any case, during the period of the long-term safety study, where patients are not receiving additional dosing (and are waiting for ADA evaluation), these patients should be treated with standard of care as appropriate. A separate protocol was issued for the long-term safety study.</p> <p>CH attack information will be captured daily during the double-blind treatment period using an electronic diary device. Assessments of change in quality of life and health status (using the Hospital Anxiety and Depression Scale [HADS], EuroQol-5 Dimension [EQ-5D] questionnaire, 12-Item Short Form Health Survey [SF-12], Impact on Partner and Family questionnaire, and Work Productivity and Activity Impairment [WPAI] questionnaire); satisfaction with treatment (using the PPSI and Patients’ Global Impression of Change [PGIC] scale); safety evaluations (including eC-SSRS); blood collection for pharmacokinetic, immunogenicity, biomarker, and pharmacogenomic (unless not allowed per local regulation) analyses; and urine sampling for biomarker analysis will be performed at prespecified time points.</p>	<p>opportunity to participate in the long-term safety study either for treatment and long-term safety assessment or for long-term safety assessment alone.</p>

Original text with changes shown	New wording	Reason/justification for change
[PGIC] scale); safety evaluations (including eC-SSRS); blood collection for pharmacokinetics, immunogenicity, biomarker, and pharmacogenomics (unless not allowed per local regulation) analyses; and urine sampling for biomarker analysis will be performed at prespecified time points.		
<b>Section 3.4, Stopping Rules for the Study (other section affected by this change: Section 4.3, Withdrawal Criteria and Procedures)</b>		
<ul style="list-style-type: none"> <li>The interim analysis (performed when 50% of patients have completed 4-week assessments during the double-blind study period <u>or have withdrawn from the study early</u>) supports stopping early for futility.</li> </ul>	<ul style="list-style-type: none"> <li>The interim analysis (performed when 50% of patients have completed 4-week assessments during the double-blind study period or have withdrawn from the study early) supports stopping early for futility.</li> </ul>	Added clarification regarding the timing of the interim analysis
The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, <u>lack of efficacy</u> , protocol deviation as defined in Section 10, noncompliance, or adverse event).	The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation as defined in Section 10, noncompliance, or adverse event).	Added clarification that lack of efficacy may result in withdrawal from the study.
<b>Section 3.5, Table 2: Study Procedures and Assessments (other section affected by this change: Appendix B, Study Procedures and Assessments by Visit)</b>		
Week 12 - EOT or early withdrawal day 84 (±3 days) Removed “Hypersensitivity/anaphylaxis reaction assessment” time point from the table		Hypersensitivity/ana phylaxis reaction assessment removed because there is no IMP administration at this visit.
<b>Section 4, Selection and Withdrawal of Patients</b>		
Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by the sponsor (Appendix C). <u>Any deviation from the eligibility criteria will result in study drug discontinuation in the event that a patient has not been dosed.</u>	Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by the sponsor (Appendix C). Any deviation from the eligibility criteria will result in study drug discontinuation in the event that a patient has not been dosed.	Updated for clarification.
<b>Section 4.1, Patient Inclusion Criteria (other section affected by this change: Appendix H, Preventive Cluster Headache Medications and Disallowed Medications)</b>		
e. The patient is not using or using <del>≤ a maximum of 2</del> concomitant medications that are commonly prescribed as	e. The patient is not using or using ≤2 concomitant medications that are commonly prescribed as	Updated for clarification.

Original text with changes shown	New wording	Reason/justification for change
<p>preventive treatments for CH (Appendix H), regardless of the indication for which the medication was prescribed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.</p>	<p>preventive treatments for CH (Appendix H), regardless of the indication for which the medication was prescribed. Patients must be on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.</p>	
<p>f. <u>If a patient is receiving Botox, it should be in a stable dose regimen, considered as having ≥2 cycles of Botox prior to screening. The patient should not receive Botox during the run-in period up to the evaluation period (12 weeks) where the primary endpoint is evaluated.</u></p>	<p>f. If a patient is receiving Botox, it should be in a stable dose regimen, considered as having ≥2 cycles of Botox prior to screening. The patient should not receive Botox during the run-in period up to the evaluation period (12 weeks) where the primary endpoint is evaluated.</p>	<p>Added inclusion criterion to specify treatment window for patients that have been treated with Botox for the prevention of migraine.</p>
<p>j. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening, are sterile, or postmenopausal, <u>and are not lactating.</u> Definitions of sterile and postmenopausal are given in Appendix E.</p>	<p>j. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening, are sterile or postmenopausal, and are not lactating. Definitions of sterile and postmenopausal are given in Appendix E.</p>	<p>Updated for clarification.</p>
<p>l. Men must be sterile or, if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must <u>agree to</u> use, together with their female partners, acceptable birth control methods for the duration of the study and for 7.5 months after discontinuation of the IMP. Definitions of <del>WOCBP</del> <u>women of non-childbearing potential</u>, sterile <u>women</u>, and postmenopausal women; male contraception; and highly effective and acceptable birth control methods including examples are given in Appendix E.</p>	<p>l. Men must be sterile or, if they are potentially fertile/reproductively competent (not surgically [eg, vasectomy] or congenitally sterile) and their female partners are of childbearing potential, must agree to use, together with their female partners, acceptable birth control methods for the duration of the study and for 7.5 months after discontinuation of the IMP. Definitions of women of non-childbearing potential, sterile women, and postmenopausal women; male contraception; and highly effective and acceptable birth control methods including examples are given in Appendix E.</p>	<p>Updated for clarification.</p>
<p><b>Section 4.2, Patient Exclusion Criteria (other section affected by this change: Appendix H, Preventive Cluster Headache Medications and Disallowed Medications)</b></p>		
<p>a. The patient has used <u>systemic steroids for any medical reason (including treatment of short corticosteroid cycle to</u></p>	<p>a. The patient has used systemic steroids for any medical reason (including treatment of short corticosteroid</p>	<p>Updated for clarification.</p>



Original text with changes shown	New wording	Reason/justification for change
<del>tre</del> at the current CH cycle) <u>within ≤7 days prior to screening.</u>	cycle to treat the current CH cycle) within ≤7 days prior to screening.	
e. The patient has clinically significant hematological, renal, endocrine, <u>immunologic</u> , pulmonary, gastrointestinal, genitourinary, <u>cardiovascular</u> <del>cardiac</del> , neurologic, hepatic, or ocular disease at the discretion of the investigator.	e. The patient has clinically significant hematological, renal, endocrine, immunologic, pulmonary, gastrointestinal, genitourinary, cardiovascular, neurologic, hepatic, or ocular disease at the discretion of the investigator.	Updated for clarification.
i. <del>The patient has known infection or history of human immunodeficiency virus, tuberculosis, or chronic hepatitis B or C infection.</del>		Exclusion criterion deleted.
j. The patient has a past or current history of cancer <u>or malignant tumor</u> in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.	i. The patient has a past or current history of cancer or malignant tumor in the past 5 years, except for appropriately treated non-melanoma skin carcinoma.	Updated for clarification.
k. The patient is pregnant or <u>lactating</u> <del>nursing</del> .	j. The patient is pregnant or lactating.	Updated for clarification.
n. The patient has participated in a clinical study of a monoclonal antibody <u>within 3 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer</u> , unless it is known that the patient received placebo during the study.	m. The patient has participated in a clinical study of a monoclonal antibody within 3 months or 5 half-lives before administration of the first dose of the IMP, whichever is longer, unless it is known that the patient received placebo during the study.	Updated for clarification.
o. The patient has a history of prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab). <u>If the patient has participated in a clinical study with any of these monoclonal antibodies, it has to be confirmed that the patient received placebo in order to be eligible for this study.</u>	n. The patient has a history of prior exposure to a monoclonal antibody targeting the CGRP pathway (AMG 334, ALD304, LY2951742, or fremanezumab). If the patient has participated in a clinical study with any of these monoclonal antibodies, it has to be confirmed that the patient received placebo in order to be eligible for this study.	Updated for clarification.
v. The patient has an <u>active</u> implant for neurostimulation used in the treatment of CH.	u. The patient has an active implant for neurostimulation used in the treatment of CH.	Updated for clarification.
x. The patient has a history of alcohol <u>and/or drug abuse that in the investigator’s opinion could interfere with the study evaluations or the patient’s safety</u> <del>abuse prior to screening</del> .	w. The patient has a history of alcohol and/or drug abuse that in the investigator’s opinion could interfere with the study evaluations or the patient’s safety.	Updated for clarification.
<b>Section 4.3, Withdrawal Criteria and Procedures (other section affected by this change: Appendix C, Quality Control and Quality Assurance)</b>		

Original text with changes shown	New wording	Reason/justification for change
<p>8. <u>The investigator and/or sponsor may withdraw an individual patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation as defined in Section 10, noncompliance, or adverse event). In addition, patients with positive eC-SSRS findings or abnormal hepatic laboratory values (eg, ALT, AST, ALP, GGT, bilirubin [total, direct, or indirect], or INR) may meet criteria for discontinuation from the IMP as summarized in Appendix J.</u></p>	<p>8. The investigator and/or sponsor may withdraw an individual patient from the study at any time for any reason (eg, lack of efficacy, protocol deviation as defined in Section 10, noncompliance, or adverse event). In addition, patients with positive eC-SSRS findings or abnormal hepatic laboratory values (eg, ALT, AST, ALP, GGT, bilirubin [total, direct, or indirect], or INR) may meet criteria for discontinuation from the IMP as summarized in Appendix J.</p>	<p>Added text for clarification for reasons for withdrawal.</p>
<p><u>In the event that a patient was incorrectly randomized and has already started taking the study drug, a risk/benefit evaluation should take place between the investigator and sponsor and a strong clinical justification must be provided if the patient is not withdrawn from study drug.</u></p>	<p>In the event that a patient was incorrectly randomized and has already started taking the study drug, a risk/benefit evaluation should take place between the investigator and sponsor and a strong clinical justification must be provided if the patient is not withdrawn from study drug.</p>	<p>Added text for clarification.</p>
<p>All protocol-specified procedures/assessments should be performed at the early withdrawal visit (see Appendix B). Patients who withdraw from the study will not be replaced. <u>Patients who discontinue early for any reason will</u><del>However, they may be offered the opportunity</del><u>option to enter/enroll in the long-term safety study (Study TV48125-CNS-30058) for the purpose of evaluation of ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study. These patients will not receive any doses of fremanezumab after completing participation in the current study and should be treated with standard of care as appropriate.</u></p>	<p>All protocol-specified procedures/assessments should be performed at the early withdrawal visit (see Appendix B). Patients who withdraw from the study will not be replaced. Patients who discontinue early for any reason willHowever, they may be offered the opportunityoption to enter/enroll in the long-term safety study (Study TV48125-CNS-30058) for the purpose of evaluation of ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study. These patients will not receive any doses of fremanezumab after completing participation in the current study and should be treated with standard of care as appropriate.</p>	<p>Added text for clarification.</p>
<p><b>Section 5.1.1, Test Investigational Medicinal Product</b></p>		
<p>Fremanezumab is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor.</p>	<p>Fremanezumab is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor.</p>	<p>Revised for clarification.</p>
<p><b>Section 5.3.1 Justification for Dose of Test Investigational Medicinal Product</b></p>		

Original text with changes shown	New wording	Reason/justification for change
<p>Third, the favorable safety profile of the drug <del>and calculated safety margins based modelling and simulations</del>, as well as clinical and nonclinical safety data on exposure, suggest that the proposed doses, regimens, and routes of administration will not present any safety concerns.</p> <p>In the current study, high doses are planned for the first dose (900 mg iv or 675 mg sc) in order to provide a rapid response, especially following iv infusion where higher peak plasma concentrations (<math>C_{max}</math>) generally occur at or shortly after the end of infusion (<del>median <math>t_{max}</math> values of 1.0 to 5.0 hours after starting the iv infusion</del>) compared with <del>96 to 108 hours</del> <u>5 to 7 days</u> postdose for sc injections.</p>	<p>Third, the favorable safety profile of the drug, as well as clinical and nonclinical safety data on exposure, suggest that the proposed doses, regimens, and routes of administration will not present any safety concerns.</p> <p>In the current study, high doses are planned for the first dose (900 mg iv or 675 mg sc) in order to provide a rapid response, especially following iv infusion where higher peak plasma (<math>C_{max}</math>) generally occur at or shortly after the end of infusion compared with 5 to 7 days postdose for sc injections.</p>	<p>Revised for clarification.</p>
<p><b>Section 5.4, Treatment after the End of the Study</b></p>		
<p>Patients who successfully complete <u>the final visit of</u> this study may be offered the opportunity to enroll in the long-term safety extension study (Study TV48125-CNS-30058), which includes a treatment period lasting approximately 40 weeks.</p>	<p>Patients who successfully complete the final visit of this study may be offered the opportunity to enroll in the long-term safety extension study (Study TV48125-CNS-30058), which includes a treatment period lasting approximately 40 weeks.</p>	<p>Revised for clarification.</p>
<p><b>Section 5.9.2, Blinding and Unblinding</b></p>		
<p><u>In the event that the IRT system is not functioning for emergency unblinding, the next course of action is to contact via phone the IRT on-call customer support helpline for manual emergency unblinding.</u></p>	<p>In the event that the IRT system is not functioning for emergency unblinding, the next course of action is to contact via phone the IRT on-call customer support helpline for manual emergency unblinding.</p>	<p>Added text for clarification.</p>
<p><b>Section 6.1, Electronic Diary Device (other section affected by this change: Section 3.5, Table 2: Study Procedure and Assessments [footnote m])</b></p>		
<p><u>Patients will complete electronic headache diary entries with questions about the previous day, starting from the day after the screening visit through the end of treatment (EOT)/early withdrawal visit. The electronic headache diary device will allow entry of headache information for up to 2 days after a given day.</u></p> <p><del>On each day, the patient will be asked to record real time diary data regarding the CH attacks.</del> Patients who report a CH attack will answer questions about the attack (ie, occurrence and</p>	<p>Patients will complete electronic headache diary entries with questions about the previous day, starting from the day after the screening visit through the end of treatment (EOT)/early withdrawal visit. The electronic headache diary device will allow entry of headache information for up to 2 days after a given day.</p> <p>Patients who report a CH attack will answer questions about the attack (ie, occurrence and number of CH attacks, duration of CH attack[s], severity of CH attack[s], and</p>	<p>Revised for clarification.</p>

Original text with changes shown	New wording	Reason/justification for change
<p>number of CH attacks, duration of CH attack[s], severity of CH attack[s], and acute CH-specific medication <u>and oxygen use</u>). <u>The last day of the run-in period should be reported in the morning of the visit day.</u> <del>use) in real time or retrospectively for the previous 24-hour period.</del></p>	<p>acute CH-specific medication and oxygen use). The last day of the run-in period should be reported in the morning of the visit day.</p>	
<p>If a patient fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day’s information the next time he/she accesses the electronic diary provided no more than <del>48 hours</del> <u>2 days</u> have elapsed since completion of that day. If more than <del>48 hours</del> <u>2 days</u> have elapsed since completion of a diary day, the patient will not be allowed to enter diary information for that day, and it will be considered a missed day.</p>	<p>If a patient fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day’s information the next time he/she accesses the electronic diary provided no more than 2 days have elapsed since completion of that day. If more than 2 days have elapsed since completion of a diary day, the patient will not be allowed to enter diary information for that day, and it will be considered a missed day.</p>	<p>Revised for clarification.</p>
<p><b>Section 7.1.8, Protocol Deviations Because of an Adverse Event (other sections affected by this change: Section 7.3, Medication Error and Special Situations Related to the Investigational Medicinal Products; Appendix C, Quality Control and Quality Assurance)</b></p>		
<p>If a patient experiences an adverse event or medical emergency, deviations from the protocol may be <del>allowed on a case-by-case basis</del> <u>warranted</u> to ensure patient safety. <del>To ensure patient safety,</del> <u>After</u> the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study. <u>The same reporting process as for all other protocol deviations will apply. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol.</u></p>	<p>If a patient experiences an adverse event or medical emergency, deviations from the protocol may be warranted to ensure patient safety. After the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study. The same reporting process as for all other protocol deviations will apply. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol.</p>	<p>Revised for clarification.</p>
<p><b>Section 7.3, Medication Error and Special Situations Related to the Investigational Medicinal Products</b></p>		

Original text with changes shown	New wording	Reason/justification for change
<p>Any administration of IMP that is not in accordance with the study protocol should be reported as an important deviation, if it meets the important deviation criteria specified in the protocol (Appendix C), <u>or as a deviation</u> in the patient’s source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be reported in the clinical trial management system. <u>A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety.</u></p>	<p>Any administration of IMP that is not in accordance with the study protocol should be reported as an important deviation, if it meets the important deviation criteria specified in the protocol (Appendix C), or as a deviation in the patient’s source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be reported in the clinical trial management system. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety.</p>	<p>Revised for clarification.</p>
<p><b>Section 7.4.1, Serum Chemistry, Hematology, and Urinalysis (other sections affected by the change: Section 3.5, Table 2: Study Procedure and Assessments footnote i; Appendix B, Study Procedures and Assessments by Visit)</b></p>		
<p>Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the central laboratory. <u>However, in case of abnormal coagulation during screening (run-in period) or if other specific urgent tests are required, a local retest can be authorized by the sponsor or designee on a case-by-case basis.</u> Specific laboratory tests to be performed are provided in Appendix M.</p>	<p>Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 2. Clinical laboratory tests will be performed using the central laboratory. However, in case of abnormal coagulation during screening (run-in period) or if other specific urgent tests are required,) a local retest can be authorized by the sponsor or designee on a case-by-case basis. Specific laboratory tests to be performed are provided in Appendix M.</p>	<p>Revised for clarification.</p>
<p><b>Section 7.8, Immunogenicity</b></p>		
<p>Blood samples for serum ADA assessment will be collected at the time points detailed in Table 2. <del>Only the samples from fremanezumab treated patients will be analyzed for ADAs.</del></p>	<p>Blood samples for serum ADA assessment will be collected at the time points detailed in Table 2.</p>	<p>Revised for clarification.</p>
<p><b>Section 7.11, Injection Site Assessments (other sections affected by this change: Section 3.5, Table 2: Study Procedure and Assessments footnote z; Appendix B, Study Procedures and Assessments by Visit)</b></p>		
<p>Injection site assessments will be performed immediately (<u>+10 minutes</u>) and 1 hour (<u>±15 minutes</u>) after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, <u>and</u> ecchymosis, <del>and pain</del>. Severity will be graded according to the following criteria:</p> <ul style="list-style-type: none"> <li>• Injection site erythema, induration, and ecchymosis will</li> </ul>	<p>Injection site assessments will be performed immediately (+10 minutes) and 1 hour (±15 minutes) after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, and ecchymosis. Severity will be graded according to the following criteria:</p> <ul style="list-style-type: none"> <li>• Injection site erythema, induration, and ecchymosis</li> </ul>	<p>Added clarification for injection site assessment windows.</p>

Original text with changes shown	New wording	Reason/justification for change
<p>be graded according to measurements: absent, 5 to <math>\leq 50</math> mm (mild), <math>&gt;50</math> to <math>\leq 100</math> mm (moderate), and <math>&gt;100</math> mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.</p> <ul style="list-style-type: none"> <li>For spontaneous report of local pain after the injection, <del>it</del><del>Injection site pain</del> will be measured as summarized in Table 5.</li> </ul>	<p>will be graded according to measurements: absent, 5 to <math>\leq 50</math> mm (mild), <math>&gt;50</math> to <math>\leq 100</math> mm (moderate), and <math>&gt;100</math> mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.</p> <ul style="list-style-type: none"> <li>For spontaneous report of local pain after the injection, it will be measured as summarized in Table 5.</li> </ul>	
<p>Revised the “Assessment” column in Table 5 Severity of Pain Scale for Injection Site Assessments Severity grade 1 (mild) = Painful on touch revised to Severity grade 1 = Mild Severity grade 2 (moderate) = Pain on ambulation revised to Severity grade 2 = Moderate Severity grade 3 (severe) = Spontaneously painful revised to Severity grade 3 = Severe</p>	<p>Severity grade 1 = Mild Severity grade 2 = Moderate Severity grade 3 = Severe</p>	<p>Revised for clarification.</p>
<p>If a patient has severe injection site induration, erythema, ecchymosis, or pain at 1 hour after completion of IMP administration, the patient will be reassessed at 3 hours (<u><math>\pm 15</math> minutes</u>) after completion of IMP administration and hourly (<u><math>\pm 15</math> minutes</u>) thereafter until the reaction is of moderate or less severity.</p>	<p>If a patient has severe injection site induration, erythema, ecchymosis, or pain at 1 hour after completion of IMP administration, the patient will be reassessed at 3 hours (<math>\pm 15</math> minutes) after completion of IMP administration and hourly (<math>\pm 15</math> minutes) thereafter until the reaction is of moderate or less severity.</p>	<p>Added visit windows for clarification.</p>
<p>Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) <del>should</del><del>will also</del> be recorded as adverse events.</p>	<p>Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) should be recorded as adverse events.</p>	<p>Added for clarification.</p>
<p><b>Section 9.1, Sample Size and Power Considerations</b></p>		
<p>Assuming a 14% discontinuation rate, <u>approximately</u> 300 patients will be randomized in the trial.</p>	<p>Assuming a 14% discontinuation rate, approximately 300 patients will be randomized in the trial.</p>	<p>Revised for consistency with other sections.</p>
<p><b>Section 9.6, Multiple Comparisons and Multiplicity</b></p>		
<p>Hochberg’s step-up method will be implemented to test primary and secondary endpoints while controlling the overall type 1 error rate at 0.05. <u>The treatment comparisons will be for the fremanezumab 900-mg iv loading dose group versus</u></p>	<p>Hochberg’s step-up method will be implemented to test primary and secondary endpoints while controlling the overall type 1 error rate at 0.05. The treatment comparisons will be for the fremanezumab 900-mg iv</p>	<p>Details about multiple comparisons and multiplicity added</p>

Original text with changes shown	New wording	Reason/justification for change
<p><u>placebo [<math>H_{01}</math>] and the fremanezumab 675-mg sc quarterly group versus placebo [<math>H_{02}</math>]. According to Hochberg step-up method, the rules of multiple comparisons for 2 null hypotheses for the primary endpoint are as follows:–Details will be provided in the statistical analysis plan.</u></p> <ol style="list-style-type: none"> <li>4. <u>If the resulting 2-sided p-values from both comparisons are <math>\leq 0.05</math> (reject both null hypotheses), then the next comparison of interest will be interpreted inferentially at the alpha level of 0.05 and statistical significance will be claimed for both active dose groups. Testing of secondary efficacy measures will be continued.</u></li> <li>5. <u>If the resulting 2-sided p-value from 1 of comparisons is <math>&gt; 0.05</math> (fail to reject the null hypothesis) and the other resulting 2-sided p-value is <math>\leq 0.025</math> (<math>\alpha/2=0.025</math>; reject the null hypothesis), then the result from the comparison with p-value <math>\leq 0.025</math> will be interpreted inferentially at the alpha level of 0.05 and statistical significance will be claimed for this active dose group. No other comparison(s) will be interpreted inferentially.</u></li> <li>6. <u>If the resulting 2-sided p-values from both comparisons are <math>&gt; 0.05</math> (fail to reject both null hypotheses), then no statistical significance will be claimed and no comparisons will be interpreted inferentially.</u></li> </ol> <p><u>If the resulting 2-sided p-values from both comparisons for the primary endpoint are <math>\leq 0.05</math> (reject both hypotheses; case 1 as described above), testing of secondary efficacy measures will proceed at an error rate of 0.05 in the sequential manner as specified in Section 2.1. The same testing rules as described above will be followed. This process will continue either until all comparisons of interest for secondary endpoints are interpreted inferentially or until the point at which the</u></p>	<p>loading dose group versus placebo [<math>H_{01}</math>] and the fremanezumab 675-mg sc quarterly group versus placebo [<math>H_{02}</math>]. According to Hochberg step-up method, the rules of multiple comparisons for 2 null hypotheses for the primary endpoint are as follows:</p> <ol style="list-style-type: none"> <li>7. If the resulting 2-sided p-values from both comparisons are <math>\leq 0.05</math> (reject both null hypotheses), then the next comparison of interest will be interpreted inferentially at the alpha level of 0.05 and statistical significance will be claimed for both active dose groups. Testing of secondary efficacy measures will be continued.</li> <li>8. If the resulting 2-sided p-value from 1 of comparisons is <math>&gt; 0.05</math> (fail to reject the null hypothesis) and the other resulting 2-sided p-value is <math>\leq 0.025</math> (<math>\alpha/2=0.025</math>; reject the null hypothesis), then the result from the comparison with p-value <math>\leq 0.025</math> will be interpreted inferentially at the alpha level of 0.05 and statistical significance will be claimed for this active dose group. No other comparison(s) will be interpreted inferentially.</li> <li>9. If the resulting 2-sided p-values from both comparisons are <math>&gt; 0.05</math> (fail to reject both null hypotheses), then no statistical significance will be claimed and no comparisons will be interpreted inferentially.</li> </ol> <p>If the resulting 2-sided p-values from both comparisons for the primary endpoint are <math>\leq 0.05</math> (reject both hypotheses; case 1 as described above), testing of secondary efficacy measures will proceed at an error rate of 0.05 in the sequential manner as specified in Section 2.1. The same testing rules as described above will be followed. This process will continue either until all comparisons of interest for secondary endpoints are</p>	<p>for clarification.</p>

Original text with changes shown	New wording	Reason/justification for change
<p><u>resulting 2-sided p-value for a comparison of interest is &gt;0.05. At the point where a 2-sided p-value is &gt;0.05, the testing process stops. No further comparisons will be interpreted inferentially.</u></p>	<p>interpreted inferentially or until the point at which the resulting 2-sided p-value for a comparison of interest is &gt;0.05. At the point where a 2-sided p-value is &gt;0.05, the testing process stops. No further comparisons will be interpreted inferentially.</p>	
<p><b>Section 9.15, Planned Interim Analysis</b></p>		
<p>An interim analysis for futility will be performed once 50% of patients (<u>the first 150 patients</u>) have completed 12-week assessments during the double-blind study period <u>or have withdrawn from the study early</u>. An independent statistician from a third party will perform evaluations.</p>	<p>An interim analysis for futility will be performed once 50% of patients (the first 150 patients) have completed 4-week assessments during the double-blind study period or have withdrawn from the study early. An independent statistician from a third party will perform evaluations.</p>	<p>Revised for clarification.</p>
<p><b>Section 11, Compliance Statement</b></p>		
<p>See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and <del>IRV</del>IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.</p>	<p>See Appendix D for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.</p>	<p>Revised for correctness.</p>
<p><b>APPENDIX C, QUALITY CONTROL AND QUALITY ASSURANCE</b></p>		
<p><u>A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol.</u> Changes in the inclusion and exclusion criteria of the protocol are <b>not</b> prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol deviation. <u>A deviation from the eligibility criteria will always result in study drug discontinuation in case the patient has not been dosed. In case a patient who was wrongly randomized has already started taking the study drug, a risk/benefit evaluation has to take place and a strong clinical justification must be provided in case the patient is not withdrawn from the</u></p>	<p>A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient’s safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of Good Clinical Practice (GCP) and the protocol. Changes in the inclusion and exclusion criteria of the protocol are <b>not</b> prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol deviation. A deviation from the eligibility criteria will always result in study drug discontinuation in case the patient has not been dosed. In case a patient who was wrongly randomized has already started taking the study drug, a risk/benefit evaluation has to take place and a strong clinical justification must be</p>	<p>Revised for clarification.</p>



Original text with changes shown	New wording	Reason/justification for change
<u>study drug.</u>	provided in case the patient is not withdrawn from the study drug.	
<b>Appendix E, WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS</b>		
<p><b>Women of <u>non-childbearing potential</u> are defined as:</b></p> <ul style="list-style-type: none"> <li>• <del>not</del>Surgically (<del>documented</del> hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile</li> <li>• <u>One</u> <del>1</del>-year postmenopausal (<del>stable amenorrhea</del> <del>no</del> <del>menses</del> for 12 months without alternative medical cause plus an increased concentration of follicle-stimulating hormone (FSH) serum level in the <u>postmenopausal range of more than 35 U/L</u>) in women not using hormonal contraception or hormonal replacement therapy</li> <li>• <u>Women in stable post-menopause, but are taking hormone replacement therapy for treatment of menopausal symptoms may be considered eligible for the study even with the lower serum FSH. They do not need to use other contraception.</u></li> </ul>	<p><b>Women of non-childbearing potential are defined as:</b></p> <ul style="list-style-type: none"> <li>• Surgically (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile</li> <li>• One year postmenopausal (stable amenorrhea for 12 months without alternative medical cause plus an increased concentration of follicle-stimulating hormone (FSH) serum level in the postmenopausal range) in women not using hormonal contraception or hormonal replacement therapy</li> <li>• Women in stable post-menopause, but are taking hormone replacement therapy for treatment of menopausal symptoms may be considered eligible for the study even with the lower serum FSH. They do not need to use other contraception.</li> </ul>	Revised for clarification.
<ul style="list-style-type: none"> <li>• Bilateral tubal occlusion <del>and</del> <del>v</del>Vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.</li> </ul>	<ul style="list-style-type: none"> <li>• Bilateral tubal occlusion</li> <li>• Vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.</li> </ul>	Revised for clarification.
<b>Appendix F, LOST TO FOLLOW-UP</b>		
<p>A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and <u>if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc)</u> <del>be contacted by the investigational center.</del></p>	<p>A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).</p>	Revised for clarification.
<b>Appendix G, HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL PRODUCT(S)</b>		
<u>Preparation instructions for iv infusions: Investigational</u>	<u>Preparation instructions for iv infusions: Investigational</u>	Revised for

Original text with changes shown	New wording	Reason/justification for change
<p>medicinal product (IMP) syringes should be allowed to <u>equilibrate at room temperature for 45 to 60 minutes before administration into the iv bag.</u> The contents of 4 prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) or 1.5 mL of placebo, will be added to 500 mL of normal saline solution. The iv infusion will be administered over approximately 1 hour.</p> <p><u>Preparation instructions for sc injections:</u> IMP should be allowed to equilibrate at room temperature for <del>45-15 to 60</del><del>30</del> minutes before sc administration.</p>	<p>medicinal product (IMP) syringes should be allowed to equilibrate at room temperature for 45 to 60 minutes before administration into the iv bag. The contents of 4 prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) or 1.5 mL of placebo, will be added to 500 mL of normal saline solution. The iv infusion will be administered over approximately 1 hour.</p> <p><u>Preparation instructions for sc injections:</u> IMP should be allowed to equilibrate at room temperature for 45 to 60 minutes before sc administration.</p>	<p>correctness.</p>
<p><b>Appendix H, PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS</b></p> <p><b>2. Concomitant Medications Allowed and Disallowed</b></p>		
<p><u>Steroids:</u> The only allowed steroids are intra-articular injection or ocular, ear drops, <u>intranasal, inhaled,</u> and creams for topical use.</p> <p><u>Butalbital:</u> Screening/run-in period: Disallowed if used more than 3 days during the screening/run-in period. <u>Patients can use butalbital as needed (PRN) after randomization into the study.</u></p> <p><u>Opioids:</u> Screening/run-in period: Disallowed if used more than 4 days during the screening/run-in period. <u>Patients can use opioids PRN after randomization into the study.</u></p>	<p><u>Steroids:</u> The only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use.</p> <p><u>Butalbital:</u> Screening/run-in period: Disallowed if used more than 3 days during the screening/run-in period. Patients can use butalbital as needed (PRN) after randomization into the study.</p> <p><u>Opioids:</u> Screening/run-in period: Disallowed if used more than 4 days during the screening/run-in period. Patients can use opioids PRN after randomization into the study.</p>	<p>Revised for clarification.</p>
<p><b>Appendix L, TOTAL BLOOD VOLUME (other sections affected by this change: (Section 3.5, Table 2: Study Procedure and Assessments [footnote r]; Section 5.10, Total Blood Volume; Appendix B, Study Procedures and Assessments by Visit; Appendix P)</b></p>		
<p>The total blood volume to be collected for each patient in this study is approximately <del>131.5</del><del>118</del> mL (at maximum) for scheduled tests.</p>	<p>The total blood volume to be collected for each patient in this study is approximately 131.5 mL (at maximum) for scheduled tests.</p>	<p>Revised for clarification</p>
<p>Serum chemistry sample volume was revised from 3 to 3.5 mL (5 samples in total) with a total volume of 17.5 mL. Serum pregnancy sample volume was revised from 3 mL (5 samples in total) to 3.5 mL (2 samples in total).</p>	<p>Serum chemistry: 3.5 mL at 5 total number of samples and 17.5 mL total volume Serum pregnancy: 3.5 mL at 2 total number of samples and 7 mL total volume</p>	<p>Revised for clarification</p>

Original text with changes shown	New wording	Reason/justification for change
<p>Hematology sample volume was revised from 3 mL to 2 mL, and the total volume was changed from 15 mL to 10 mL. Coagulation sample of 4.5 mL (5 samples in total) with a total volume of 22.5 mL was added. FSH sample volume was revised from 3 mL to 3.5 mL, and the total volume was changed from 3 mL to 3.5 mL. The number of pharmacokinetic samples was decreased from 5 to 4, and the total volume was changed from 20 mL to 16 mL. Biomarker serum sample volume was revised from 14.5 mL to 8.5 mL, and the total volume was changed from 29 mL to 17 mL. Biomarker plasma sample of 6 mL (2 samples in total) with a total volume of 12 mL was added. Biomarker RNA sample was adjusted from 14.5 mL to 2.5 mL, and the total volume was changed from 29 mL to 5 mL. The total volume of sample is thus changed from 118 mL to 131.5 mL, and the total number of samples was changed from 22 to 32.</p>	<p>Hematology: 2 mL at 5 total number of samples and 10 mL total volume Coagulation: 4.5 mL at 5 total number of samples and 22 mL total volume FSH: 3.5 mL at 1 total number of samples and 3.5 mL total volume Pharmacokinetics: 4 mL at 4 total number of samples and 16 mL total volume Biomarker serum: 8.5 mL at 2 total number of samples and 17 mL total volume Biomarker plasma: 6 mL at 2 total number of samples and 12 mL total volume Biomarker RNA: 2.5 mL at 2 total number of samples and 5 mL total volume Total: 32 samples at 131.5 mL total volume</p>	
<p><b>Appendix N, PHARMACOKINETICS SAMPLES (other section affected by this change: Appendix O, IMMUNOGENICITY SAMPLES)</b></p>		
<p>Separated plasma will be transferred in approximately equal portions in 2 labeled <u>2-mL</u> polypropylene tubes (Sets A and B).</p>	<p>Separated plasma will be transferred in approximately equal portions in 2 labeled 2-mL polypropylene tubes (Sets A and B).</p>	<p>Revised for clarification.</p>
<p>Set A samples will be transported <u>frozen</u>, with a temperature data logger and <del>frozen</del> with dry ice sufficient for 4 days, <u>on a monthly basis by next day courier</u> to the central laboratory. <u>Central laboratory will ship the Set A samples on a monthly basis to the</u> <del>or</del> <u>bioanalytical laboratory with dry ice sufficient for 4 days and with a temperature data logger.</u> Set B samples will be sent <del>either</del> to the same laboratory as that for Set A <del>samples on a subsequent day by next day courier, or be retained at the investigational center until the study is completed and the CSR has been issued (unless shipment to another facility is requested by the sponsor).</del> Instructions as to</p>	<p>Set A samples will be transported frozen, with a temperature data logger and with dry ice sufficient for 4 days, <u>on a monthly basis to the central laboratory. Central laboratory will ship the Set A samples on a monthly basis to the</u> <del>or</del> <u>bioanalytical laboratory with dry ice sufficient for 4 days and with a temperature data logger.</u> Set B samples will be sent to the same laboratory as that for Set A. Instructions as to the disposition of the Set B samples will be provided by the sponsor.</p>	<p>Revised for clarification.</p>

Original text with changes shown	New wording	Reason/justification for change
the disposition of the Set B samples will be provided by the sponsor.		

ADA=antidrug antibody; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the plasma concentration-time curve; AUC<sub>0-∞</sub>=area under the plasma concentration-time curve from 0 to infinity; CH=cluster headache; CGRP= calcitonin gene related peptide; CL/F= apparent total plasma clearance (except for metabolites); C<sub>max</sub>=maximum observed concentration; CSR=clinical study report; ECH=episodic cluster headache; EOT=end of treatment; FSH=follicle-stimulating hormone; GCP=Good Clinical Practice; GGT=gamma-glutamyl transpeptidase; IMP=investigational medicinal product; INR=international normalized ratio; IRT=interactive response technology; iv=intravenous; PRN=as needed; sc=subcutaneous; RNA=ribonucleic acid; t<sub>max</sub>=time to maximum observed concentration; V<sub>z</sub>/F=apparent total volume of distribution (except for metabolites); WOCBP=women of childbearing potential.

## **16.2. Amendment 01 Dated 30 November 2016**

The primary reason for this amendment is to update the primary endpoint based on feedback from regulatory agencies and the sample size for this study based on the new primary endpoint. This amendment is considered to be substantial (ie, requires approval by competent authorities, IEC, and/or IRB) by the sponsor's Authorized Representative. This amendment also incorporates changes detailed in the letter of clarification 01 (Section 16.4), letter of clarification 02 (Section 16.3), and letter of clarification 03 (Section 16.2) and other nonsubstantial changes. These changes are unlikely to affect the safety or rights (physical or mental integrity) of the patients in this clinical study or the scientific value of the clinical study.

[Table 2](#) (Study Procedures and Assessments) has been revised to reflect changes described below.

Original text with changes shown	New wording	Reason/Justification for change
<b>Global change (except for protocol title)</b>		
<del>fremanezumab</del> TEV 48125	fremanezumab	Generic name will now be used rather than the Teva-assigned number.
<b>Section 2.1, Primary and Secondary Study Objectives and Endpoints (other sections affected by this change: Section 9.5.1, Primary Endpoint and Section 9.5.2, Secondary Endpoints)</b>		
<p>The primary efficacy endpoint of this study is <del>the mean change from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks during the 12-week period after administration of the first dose of the investigational medicinal product (IMP), ie, based on week 0 to 12 data</del> <u>proportion of patients with a <math>\geq 50\%</math> reduction from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data.</u></p>	<p>The primary efficacy endpoint of this study is the mean change from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks during the 12-week period after administration of the first dose of the investigational medicinal product (IMP), ie, based on week 0 to 12 data.</p>	<p>The primary endpoint was updated based on feedback from regulatory agencies.</p>
<p>The secondary efficacy endpoints to further demonstrate efficacy are:</p> <ul style="list-style-type: none"> <li>• <del>the proportion of patients with a <math>\geq 50\%</math> reduction from baseline (run-in period) in the monthly average number of cluster headache (CH) attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data</del></li> <li>• ...</li> <li>• <del>the mean change from baseline (run-in period) in the number of CH attacks during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</del></li> </ul>	<p>The secondary efficacy endpoints to further demonstrate efficacy are:</p> <ul style="list-style-type: none"> <li>• the proportion of patients with a <math>\geq 50\%</math> reduction from baseline (run-in period) in the monthly average number of CH attacks over the 12-week period after the administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> </ul>	<p>The first secondary endpoint is now the primary endpoint. The endpoint that was previously the primary endpoint is now a secondary endpoint.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 2.2.1 Exploratory Objectives and Endpoints (other section affected by this change: Section 9.5.3, Exploratory Endpoints):</b>		
<ul style="list-style-type: none"> <li>mean change from baseline (run-in period) in the number of CH attacks during weeks 1, <u>2</u>, <u>3</u>, 4, 8, and 12, after administration of the first dose of the IMP</li> </ul>	<ul style="list-style-type: none"> <li>mean change from baseline (run-in period) in the number of CH attacks during weeks 1, 2, 3, 4, 8, and 12, after administration of the first dose of the IMP</li> </ul>	<p>Analyses were added for additional time points at weeks 2 and 3 to further explore the time to the onset of treatment effect.</p>
<ul style="list-style-type: none"> <li><u>mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the second dose of the IMP, ie, based on week 4 to 8 data</u></li> </ul>	<ul style="list-style-type: none"> <li>mean change from baseline (run-in period) in the number of CH attacks during the 4-week period after administration of the second dose of the IMP, ie, based on week 4 to 8 data</li> </ul>	<p>An endpoint to assess the efficacy during the second month of treatment to further explore the time course and to explore maintenance of efficacy during the second month of treatment.</p>
<ul style="list-style-type: none"> <li><del>mean</del> change from baseline (run-in period) in the severity of CH attacks (<u>mild, moderate, severe, or very severe</u>) during weeks 1, <u>2</u>, <u>3</u>, 4, 8, and 12 <del>as measured by the NRS 11</del>, after administration of the first dose of the IMP</li> </ul>	<ul style="list-style-type: none"> <li>change from baseline (run-in period) in the severity of CH attacks (mild, moderate, severe, or very severe) during weeks 1, 2, 3, 4, 8, and 12 after administration of the first dose of the IMP</li> </ul>	<p>Severity will no longer be recorded numerically using the NRS scale. The scale to be used is categorical, and consequently “mean” is no longer applicable. Finally, analyses were added at weeks 2 and 3 to further explore the onset of treatment effect.</p>
<ul style="list-style-type: none"> <li><u>total cumulative distribution of percent reduction (<math>\geq 0\%</math>, <math>\geq 10\%</math>, <math>\geq 20\%</math>, <math>\geq 30\%</math>, <math>\geq 40\%</math>, <math>\geq 50\%</math>, <math>\geq 60\%</math>, <math>\geq 70\%</math>, or <math>\geq 80\%</math>) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data</u></li> <li><u>cumulative distribution function plot of percent reduction (<math>\geq 0\%</math>, <math>\geq 10\%</math>, <math>\geq 20\%</math>, <math>\geq 30\%</math>, <math>\geq 40\%</math>, <math>\geq 50\%</math>, <math>\geq 60\%</math>, <math>\geq 70\%</math>, or <math>\geq 80\%</math>) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data</u></li> </ul>	<ul style="list-style-type: none"> <li>total cumulative distribution of percent reduction (<math>\geq 0\%</math>, <math>\geq 10\%</math>, <math>\geq 20\%</math>, <math>\geq 30\%</math>, <math>\geq 40\%</math>, <math>\geq 50\%</math>, <math>\geq 60\%</math>, <math>\geq 70\%</math>, or <math>\geq 80\%</math>) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP, ie, based on week 0 to 12 data</li> <li>cumulative distribution function plot of percent reduction (<math>\geq 0\%</math>, <math>\geq 10\%</math>, <math>\geq 20\%</math>, <math>\geq 30\%</math>, <math>\geq 40\%</math>, <math>\geq 50\%</math>, <math>\geq 60\%</math>, <math>\geq 70\%</math>, or <math>\geq 80\%</math>) from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after the first dose of the IMP,</li> </ul>	<p>Added 3 more exploratory endpoints to further evaluate the efficacy of fremanizumab.</p>

Original text with changes shown	New wording	Reason/Justification for change
<ul style="list-style-type: none"> <li>• <u>mean change from baseline (run-in period) in the monthly average number of CH attacks of at least severe severity during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</u></li> </ul>	<p>ie, based on week 0 to 12 data</p> <ul style="list-style-type: none"> <li>• mean change from baseline (run-in period) in the monthly average number of CH attacks of at least severe severity during the 12-week period after administration of the first dose of the IMP, ie, based on week 0 to 12 data</li> </ul>	
<p><b>Section 2.2.2, Wearable Sensor Substudy Exploratory Objectives and Endpoints (other section affected by the change: Section 9.5.3, Exploratory Endpoints)</b></p>		
<ul style="list-style-type: none"> <li>• to evaluate changes in <del>physical movements</del><u>attacks</u> during days patients experience CH attacks relative to days free of attacks</li> <li>• to determine the relationship between <del>physical movements</del><u>attacks</u> and sleep pattern and the frequency of CH attacks</li> <li>• to determine the relationship between <del>physical movements</del><u>attacks</u> and sleep pattern and the intensity of CH attacks</li> <li>• to determine the relationship between <del>physical movements</del><u>attacks</u> and sleep pattern and the duration of CH attacks</li> <li>• to explore the differences in <del>physical movements</del><u>attacks</u> and sleep pattern in patients with CCH</li> <li>• to examine the relationship between <del>physical movements</del><u>attacks</u> and sleep pattern and that of genetic and biomarker measures</li> <li>• to evaluate changes in <del>physical movements</del><u>attacks</u> in predicting seasonal</li> </ul>	<ul style="list-style-type: none"> <li>• to evaluate changes in attacks during days patients experience CH attacks relative to days free of attacks</li> <li>• to determine the relationship between attacks and sleep pattern and the frequency of CH attacks</li> <li>• to determine the relationship between attacks and sleep pattern and the intensity of CH attacks</li> <li>• to determine the relationship between attacks and sleep pattern and the duration of CH attacks</li> <li>• to explore the differences in attacks and sleep pattern in patients with CCH</li> <li>• to examine the relationship between attacks and sleep pattern and that of genetic and biomarker measures</li> <li>• to evaluate changes in attacks in predicting seasonal onset of new CH episode</li> </ul>	<p>Changed to align with how the Phillips device reports activity.</p>



Original text with changes shown	New wording	Reason/Justification for change
<p>onset of new CH episode</p>		
<ul style="list-style-type: none"> <li>• the change in the total time of sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity before (6-hour period), during, and after (6-hour period) CH attack relative to days free of attacks</li> <li>• the correlation between total time in sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the frequency of CH attacks</li> <li>• the correlation between total time in sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache intensity during CH <del>incidents</del><u>attacks</u></li> <li>• the correlation between total time in sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache duration during CH <del>incidents</del><u>attacks</u></li> <li>• the average total time in sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency in patients with CCH</li> <li>• the correlation between the total time in sedentary, light, moderate, <del>intense, and very intense</del> and <u>vigorous</u> activity; total sleep time; sleep onset latency; wake after sleep onset;</li> </ul>	<ul style="list-style-type: none"> <li>• the change in the total time of sedentary, light, moderate, and vigorous activity before (6-hour period), during, and after (6-hour period) CH attack relative to days free of attacks</li> <li>• the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and the frequency of CH attacks</li> <li>• the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache intensity during CH attacks</li> <li>• the correlation between total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency and headache duration during CH attacks</li> <li>• the average total time in sedentary, light, moderate, and vigorous activity; total sleep time; sleep onset latency; wake after sleep onset; and sleep efficiency in patients with CCH</li> <li>• the correlation between the total time in sedentary, light, moderate, and vigorous activity; total sleep time;</li> </ul>	<p>Changed to align with how the Phillips device reports activity. Phillips device does no report steps.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>and sleep efficiency and the genetic and biomarker profiles</p> <ul style="list-style-type: none"> <li><del>the change in total time in sedentary, light, moderate, intense, and very intense activity and total number of steps during the remission period of patients with CCH and 15 days preceding a new epoch of CH attacks</del></li> <li>detection of time-dependent patterns composed of lower- and higher-level activity <del>matrices</del>metrics (eg, activity score, <del>and sleep/wake patterns, and physical movements</del>)</li> </ul>	<p>sleep onset latency; wake after sleep onset; and sleep efficiency and the genetic and biomarker profiles</p> <ul style="list-style-type: none"> <li>detection of time-dependent patterns composed of lower- and higher-level activity metrics (eg, activity score and sleep/wake patterns)</li> </ul>	
<b>Section 3.1, General Design and Study Schematic Diagram</b>		
<p>The study will consist of a screening visit, a run-in period lasting approximately 4 weeks (+3 days), and a 12-week double-blind treatment period. <u>During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.</u></p>	<p>The study will consist of a screening visit, a run-in period lasting approximately 4 weeks (+3 days), and a 12-week double-blind treatment period. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.</p>	<p>Added sentence to emphasize/clarify that acute medications are allowed.</p>
<p>Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit for this study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon satisfactory completion of the final study assessments, patients <del>will</del>may be offered <u>the opportunity</u> to enter a 68-week long-term safety study (Study TV48125-CNS-30058), consisting of a 40-week long-term treatment period and a final follow-up visit approximately 7.5 months after the last dose of the IMP. A separate protocol will be issued for the long-term safety study. Patients who do not enroll in</p>	<p>Blinded treatment will be administered once monthly (ie, approximately every 4 weeks) for a total of 3 months. Final study assessments will be performed at the final visit for this study (visit 5), approximately 12 weeks after administration of the first dose of the IMP. Upon satisfactory completion of the final study assessments, patients may be offered the opportunity to enter a 68-week long-term safety study (Study TV48125-CNS-30058), consisting of a 40-week long-term treatment period and a final follow-up visit approximately 7.5 months after the last dose of</p>	<p>Edited to allow flexibility regarding enrollment in the long-term safety study.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>the long-term safety study for any reason <del>will</del><u>may</u> be offered the opportunity to enter the study for the purpose of evaluating ADAs, <u>fremanezumab</u><del>FEV-48125</del> concentrations, and safety (adverse events and concomitant medications) at approximately 7.5 months after receiving the last dose of the IMP.</p>	<p>the IMP. A separate protocol will be issued for the long-term safety study. Patients who do not enroll in the long-term safety study for any reason may be offered the opportunity to enter the study for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) at approximately 7.5 months after receiving the last dose of the IMP.</p>	
<p>Figure 1 was updated to show <u>PBO SC</u> and <u>PBO IV</u> at the first dosing visit (visit 2) for each of the active treatment groups.</p>	<p>PBO SC PBO IV</p>	<p>Update made to clarify how blinding will be maintained.</p>
<p>A subset of patients in <del>US-based</del><u>selected</u> investigational sites will be offered <u>the opportunity</u> to participate in a substudy to understand the utility of physiological biomarker measures captured through wearable digital sensor devices as tools to monitor response to treatment and disease symptoms (eg, activity/sleep disruption).</p>	<p>A subset of patients in selected investigational sites will be offered the opportunity to participate in a substudy to understand the utility of physiological biomarker measures captured through wearable digital sensor devices as tools to monitor response to treatment and disease symptoms (eg, activity/sleep disruption).</p>	<p>There is a possibility that patients at ex-US sites may be offered the opportunity to participate in the wearable sensor substudy. The text has been revised to reflect this possibility.</p>
<p><b>Section 3.2, Planned Number of Patients and Countries</b></p>		
<p>A total of approximately <del>216300</del><u>300</u> patients (approximately <del>72100</del> patients per treatment group) are planned to be enrolled in this study. The study is planned to be conducted in <u>approximately 12</u><del>45</del> countries in approximately <del>8060</del> investigational centers. The study is expected to start in Q4/2016 and last until approximately Q3/2018.</p>	<p>A total of approximately 300 patients (approximately 100 patients per treatment group) are planned to be enrolled in this study. The study is planned to be conducted in approximately 12 countries in approximately 80 investigational centers. The study is expected to start in Q4/2016 and last until approximately Q3/2018.</p>	<p>The sample size was increased based on the new primary endpoint and decision not to re-estimate the sample size as part of the interim analysis. The number of investigational centers was increased based on the increased sample size, and the number of countries has been reduced based on feasibility assessments.</p>
<p><b>Section 3.4, Stopping Rules for the Study (other section affected by this change: Appendix C, Quality Control and Quality Assurance)</b></p>		
<p>The investigator and/or sponsor can withdraw a</p>	<p>The investigator and/or sponsor can withdraw</p>	<p>Change to terminology (violation</p>

Original text with changes shown	New wording	Reason/Justification for change
patient from the study at any time for any reason (eg, protocol <del>violation</del> or deviation as defined in Section 10, noncompliance, or adverse event).	a patient from the study at any time for any reason (eg, protocol deviation as defined in Section 10, noncompliance, or adverse event).	changed to deviation) to align with guidance from the ICH.
Patients who are discontinued early for any reason <del>will</del> may be offered the option to enroll in Study TV48125-CNS-30058 for the purpose of evaluating ADAs, <del>fremanezumab</del> TEV-48125 concentrations, and safety (adverse events and concomitant medications).	Patients who are discontinued early for any reason may be offered the option to enroll in Study TV48125-CNS-30058 for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications).	Edited to allow flexibility regarding enrollment in the long-term safety study.
<b>Section 3.5, Schedule of Study Procedures and Assessments</b>		
n. <u>The blood sample for pharmacokinetics analysis collected immediately before the end of the infusion at visit 2 (week 0) should be collected from the arm that is not used for the IMP infusion.</u> <del>Blood samples for pharmacokinetics analysis will be collected from the arm that is not used for the IMP infusion prior to dosing and immediately before the end of the infusion at visit 2 (week 0).</del> <u>All other</u> At each visit thereafter, a single blood samples for pharmacokinetics analysis will be collected prior to dosing (where applicable) and may be collected from either arm.	n. The blood sample for pharmacokinetics analysis collected immediate before the end of the infusion at visit 2 (week 0) should be collected from the arm that is not used for the IMP infusion. All other blood samples for pharmacokinetics analysis will be collected prior to dosing (where applicable) and may be collected from either arm.	With the exception of the blood sample collected immediately before the end of the IMP infusion (must be collected from the arm that is not used for the IMP infusion), blood samples for pharmacokinetics analysis may be collected from either arm.
<b>Section 4.2, Patient Exclusion Criteria</b>		
b. The patient reports using butalbital on more than <del>10</del> 7 days during the 4 weeks prior to screening or using butalbital on more than 10 days during the screening/run-in period.	b. The patient reports using butalbital on more than 10 days during the 4 weeks prior to screening or using butalbital on more than 10 days during the screening/run-in period.	Update made to align the 4-week period before the run-in with the run-in period.
h. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia], peripheral extremity ischemia, or other	h. The patient has a history of clinically significant cardiovascular disease or vascular ischemia (such as myocardial, neurological [eg, cerebral ischemia],	Time period expanded as it is important to include patients with CH who are otherwise healthy.

Original text with changes shown	New wording	Reason/Justification for change
<p>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 <del>in the last 2 years.</del></p>	<p>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.</p>	
<p><b>Section 4.3, Withdrawal Criteria and Procedures</b></p>		
<p>Patients who withdraw from the study will not be replaced. However, they <del>will</del> <u>may</u> be offered the option to enroll in Study TV48125-CNS-30058 for the purpose of evaluation of ADAs, <del>TEV 48125</del> <u>fremanezumab</u> concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study.</p>	<p>Patients who withdraw from the study will not be replaced. However, they may be offered the option to enroll in Study TV48125-CNS-30058 for the purpose of evaluation of ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study.</p>	<p>Edited to allow flexibility regarding enrollment in the long-term safety study.</p>
<p><b>Section 5.4, Treatment after the End of the Study (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)</b></p>		
<p>Patients who successfully complete this study <del>will</del> <u>may</u> be offered <u>the opportunity</u> to enroll in the long-term safety extension study (Study TV48125-CNS-30058), which includes a treatment period lasting approximately 40 weeks. <del>These patients will, therefore have continued access to TEV 48125 for up to 40 additional weeks after completing the final visit of this study.</del> Patients who do not enroll in this long-term study for any reason <del>will</del> <u>may</u> be offered the option to enter the study for the purpose of evaluating ADAs, <del>TEV 48125</del> <u>fremanezumab</u> concentrations, and safety (adverse events and concomitant medications) at approximately 7.5 months after administration of the last dose of the IMP.</p>	<p>Patients who successfully complete this study may be offered the opportunity to enroll in the long-term safety extension study (Study TV48125-CNS-30058), which includes a treatment period lasting approximately 40 weeks. Patients who do not enroll in this long-term study for any reason may be offered the option to enter the study for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) at approximately 7.5 months after administration of the last dose of the IMP.</p>	<p>Edited to allow flexibility regarding enrollment in the long-term safety study.</p>

Original text with changes shown	New wording	Reason/Justification for change
<b>Section 5.6, Prior and Concomitant Medication or Treatment</b>		
A maximum of 2 concomitant preventive medications for <del>CCH</del> are allowed.	A maximum of 2 concomitant preventive medications for CCH are allowed.	Corrected to align with the patient population in this study.
<b>Section 5.10, Total Blood Volume (other sections affected by this change: Section 3.5, Schedule of Procedures and Assessments and Appendix L, Total Blood Volume)</b>		
The total blood volume to be collected for each patient enrolling in this study <del>for treatment with TEV 48125</del> is approximately 11826 mL for scheduled tests. <u>An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed in Appendix J.</u>	The total blood volume to be collected for each patient enrolling in this study is approximately 118 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed in Appendix J.	The PAXGene RNA sample will be collected into the PAXGene RNA tube, which requires 2.5 mL of blood. The blood volume was updated from 6.5 mL to 2.5 mL to reflect this. Since 2 PAXGene RNA samples are to be collected, the total blood volume is reduced by 8 mL.  This text was also updated to clarify that blood will be collected from all patients regardless of treatment, and additional blood may be collected in the case of elevated liver function tests as detailed in Appendix J.
<b>Section 6.1, Electronic Diary Device</b>		
If a patient fails to complete the diary for the preceding day <del>within the allowed timeframe (until 00:00 hours of the latter day)</del> , <u>the patient will be prompted to enter the missed day’s information the next time he/she accesses the electronic diary provided no more than 48 hours have elapsed since completion of that day. If more than 48 hours have elapsed since completion of a diary day, the patient will not be allowed to enter diary information for that day</u> <del>the missed day’s information</del> , and it will be considered a missed day.	If a patient fails to complete the diary for the preceding day, the patient will be prompted to enter the missed day’s information the next time he/she accesses the electronic diary provided no more than 48 hours have elapsed since completion of that day. If more than 48 hours have elapsed since completion of a diary day, the patient will not be allowed to enter diary information for that day, and it will be considered a missed day.	The window of time to complete the diary entry has been extended to enable more flexibility for CH patients due to the severity of the disease.

Original text with changes shown	New wording	Reason/Justification for change
<p>If a CH is reported, then CH intensity will be subjectively rated by the patient <u>as follows</u>:<del>using NRS 11 rating scale.</del></p> <ul style="list-style-type: none"> <li>• <u>Mild</u></li> <li>• <u>Moderate</u></li> <li>• <u>Severe</u></li> <li>• <u>Very severe</u></li> </ul>	<p>If a CH is reported, then CH intensity will be subjectively rated by the patient as follows:</p> <ul style="list-style-type: none"> <li>• Mild</li> <li>• Moderate</li> <li>• Severe</li> <li>• Very severe</li> </ul>	<p>Removed the NRS scale to meet the definition of the IHS for CH attack.</p>
<p><b>Section 6.2, Numeric Rating Scale (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)</b></p>		
<p><del>6.2. Numeric Rating Scale</del> The NRS 11 is an 11-point scale for patient self-reporting of pain. The numeric scale ranges from '0' representing "no pain" to '10' representing "pain as bad as you can imagine" or "worst pain imaginable". Patients will complete the NRS 11 questionnaire in the electronic diary for each attack throughout the run-in and treatment periods (ie, through the end of treatment [EOT]; visit 5).</p>		<p>Removed the NRS scale to meet the definition of the IHS for CH attack.</p>
<p><b>Section 6.7, Patient-Perceived Satisfactory Improvement (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)</b></p>		
<p>New section number due to removal of Section 6.2: Section 6.7<del>8</del>, Patient-Perceived Satisfactory Improvement</p> <p>The PPSI was developed by ten Klooster et al (2006) and is composed of an unmarked 100 mm visual analog scale for pain intensity (VAS-P) and was adjusted for CH symptoms improvement with "no pain" and "unbearable pain" as anchors and a question regarding change in pain intensity. Patients will mark the level of CH-associated pain and indicate if pain is "<u>much worse</u>," "<u>moderately worse</u>," "<u>slightly worse</u>," "unchanged,"</p>	<p>Section 6.7, Patient-Perceived Satisfactory Improvement</p> <p>The PPSI was developed by ten Klooster et al (2006) for pain intensity and was adjusted for CH symptoms improvement. Patients will mark the level of CH-associated pain and indicate if pain is "much worse," "moderately worse," "slightly worse," "unchanged," "slightly improved," "moderately improved," or "much improved" compared with 4 weeks ago. PPSI will be defined as the change in pain that corresponds with a minimal rating of</p>	<p>In the e-diary, a VAS cannot be used. Understanding that CH causes pain, the report to measure improvement or not is adapted for CH.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p><del>“unsatisfactory</del>slightly improved,”  <del>“satisfactory</del>moderately improved,” or “good to very good”  <del>much</del> improved” compared with <del>baseline (visit 2 [day 0])</del>4 weeks ago. PPSI will be defined as the change in pain <del>on the VAS-P</del> that corresponds with a minimal rating of <del>“satisfactory</del>slightly improved.”</p>	<p>“slightly improved.”</p>	
<p><b>Section 6.8, Patient Global Impression of Change Scale</b></p>		
<p>New section number due to removal of Section 6.2: Section 6.8, Patient Global Impression of Change Scale</p> <p>Patients will rate <u>the change in their overall health and wellbeing</u> <del>how they feel during assigned time points</del> compared with how they felt <del>before receiving IMP</del> at the start of the study (the time after the patient received the first IMP dose) <del>on a 7 point scale, where 1 is</del> “much worse,” “moderately worse,” “slightly worse,” “stayed the same,” “a little better,” “moderately better,” or “much better.” <del>no change (or condition has got worse),” 4 is “somewhat better, but the change has not made any real difference,” and 7 is “a great deal better, and a considerable improvement that has made all the difference.”</del></p>	<p>New section number due to removal of Section 6.2: Section 6.8, Patient Global Impression of Change Scale</p> <p>Patients will rate the change in their overall health and wellbeing compared with how they felt at the start of the study (the time after the patient received the first IMP dose) as “much worse,” “moderately worse,” “slightly worse,” “stayed the same,” “a little better,” “moderately better,” or “much better.”</p>	<p>Updated the text to align with the e-diary.</p>
<p><b>Section 7.1.3, Severity of an Adverse Event</b></p>		
<p>For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), refer to Section 7.11.</p>	<p>For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), refer to Section 7.11.</p>	<p>Added reference to Section 7.11 to clarify how local tolerability findings will be graded.</p>
<p><b>Section 7.3 Medication Error and Special Situations Related to the Investigational Medicinal Products (other section affected by this change: Appendix C, Quality Control and Quality Assurance)</b></p>		
<p>Any administration of IMP that is not in accordance with the study protocol should be reported <del>on the CRF</del> either as an <u>important deviation</u> <del>violation</del>, if it meets the <u>important deviation</u> <del>violation</del> criteria</p>	<p>Any administration of IMP that is not in accordance with the study protocol should be reported as an important deviation, if it meets the important deviation criteria specified in the</p>	<p>Change to terminology (violation to deviation) to align with guidance from the ICH. In addition, the CRF will no longer be used to record protocol</p>



Original text with changes shown	New wording	Reason/Justification for change
<p>specified in the protocol (Appendix C), <del>or as a deviation</del>, in the patient’s source documents, regardless of whether or not an adverse event occurs as a result. When meeting <u>important</u> <del>violation-deviation</del> protocol criteria, all instances of incorrect IMP administration should be <del>categorized</del> <u>reported in the clinical trial management system on the CRF as “Non-Compliance to IMP.”</u></p>	<p>protocol (Appendix C), in the patient’s source documents, regardless of whether or not an adverse event occurs as a result. When meeting important protocol deviation criteria, all instances of incorrect IMP administration should be reported in the clinical trial management system.</p>	<p>deviation information.</p>
<p><b>Section 7.8, Immunogenicity (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)</b></p>		
<p>Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction <u>and</u> <del>(eg,</del> anaphylaxis).</p>	<p>Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis.</p>	<p>Correction to align with the rest of the protocol.</p>
<p>Bioanalytical personnel should be made aware of anaphylaxis occurrence as soon as possible in case an anti-<del>fremanezumab</del> <u>TEV-48125</u> IgE assay is needed. Patients who will not enroll in the double-blind, long-term safety study for any reason <del>will</del> <u>may</u> be offered <u>the option</u> to enter the long-term safety study for the purpose of evaluating ADAs, <del>fremanezumab</del> <u>TEV-48125</u> concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study.</p>	<p>Bioanalytical personnel should be made aware of anaphylaxis occurrence as soon as possible in case an anti-fremanezumab IgE assay is needed. Patients who will not enroll in the double-blind, long-term safety study for any reason may be offered the option to enter the long-term safety study for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) approximately 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of IMP in this study.</p>	<p>Edited to allow flexibility regarding enrollment in the long-term safety study.</p>
<p><b>Section 7.9, Assessment of Suicidality</b></p>		
<p>A positive finding will be defined as a <u>current suicide ideation with some intent to act and no plan. The investigator, based on his medical judgment, score <math>\geq 4</math> for suicidal ideation and/or a suicide attempt. If the patient scores a 4 for suicidal ideation, then the investigator</u> will determine if <u>the patient</u> should be</p>	<p>A positive finding will be defined as a current suicide ideation with some intent to act and no plan. The investigator, based on his medical judgment, will determine if the patient should be seen by a mental health specialist and if he/she should continue participating in the</p>	<p>Adapted text to the eC-SSRS electronic questionnaire format.</p>

Original text with changes shown	New wording	Reason/Justification for change												
<p>seen by a mental health specialist and if he/she should continue participating in the study. <u>If a patient reports current suicide ideation with specific plan and intent</u><del>If the patient scores a 5 for suicidal ideation and/or there is a suicide attempt</del>, then the patient should be immediately discontinued from the study and seen by a mental health specialist.</p> <p><u>Any patient should be excluded if any suicidal behaviors are reported.</u></p> <p><u>Any patient with lifetime behaviors (actual, interrupted, and aborted attempts and preparatory actions) should be excluded and/or discontinued from the study.</u></p>	<p>study. If a patient reports current suicide ideation with specific plan and intent, then the patient should be immediately discontinued from the study and seen by a mental health specialist.</p> <p>Any patient should be excluded if any suicidal behaviors are reported.</p> <p>Any patient with lifetime behaviors (actual, interrupted, and aborted attempts and preparatory actions) should be excluded and/or discontinued from the study.</p>													
<p><b>Section 7.11, Injection Site Assessments (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)</b></p>														
<p>Injection site assessments will be performed immediately and 1 hour after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain.<del>;</del><del>and</del></p> <p><del>S</del>Severity will be graded according to the following criteria:</p> <ul style="list-style-type: none"> <li>Injection-site erythema, <del>injection-site</del> induration, and <del>injection-site</del> ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), &gt;50 to ≤100 mm (moderate), and &gt;100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.</li> <li>...</li> </ul> <table border="1" data-bbox="191 1268 821 1406"> <thead> <tr> <th>Symptom</th> <th>Severity Grade</th> <th>Assessment</th> </tr> </thead> <tbody> <tr> <td>Pain</td> <td>0</td> <td><del>Absent</del>No pain</td> </tr> </tbody> </table>	Symptom	Severity Grade	Assessment	Pain	0	<del>Absent</del> No pain	<p>Injection site assessments will be performed immediately and 1 hour after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain.</p> <p>Severity will be graded according to the following criteria:</p> <ul style="list-style-type: none"> <li>Injection-site erythema, induration, and ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), &gt;50 to ≤100 mm (moderate), and &gt;100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.</li> <li>...</li> </ul> <table border="1" data-bbox="850 1333 1402 1421"> <thead> <tr> <th>Symptom</th> <th>Severity grade</th> <th>Assessment</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Symptom	Severity grade	Assessment				<p>Deleted grade 4 to align severity grading with severity scale for adverse events.</p>
Symptom	Severity Grade	Assessment												
Pain	0	<del>Absent</del> No pain												
Symptom	Severity grade	Assessment												

Original text with changes shown			New wording			Reason/Justification for change
	1 (mild)	<del>Painful on touch</del> Mild	Pain	0	Absent	
	2 (moderate)	<del>Pain on ambulation</del> Moderate		1 (mild)	Painful on touch	
	3 (severe)	<del>Spontaneously painful</del> Severe		2 (moderate)	Pain on ambulation	
	4	<del>Worst possible</del>		3 (severe)	Spontaneous ly painful	
<p>If a patient has severe injection site induration, erythema, <del>and/or</del> ecchymosis, <del>and/or</del> grade 3 (severe) or grade 4 (worst possible) injection site pain at 1 hour after <u>completion of the</u> IMP administration, the patient will be reassessed at 3 hours after <u>completion of receiving the IMP administration</u> and hourly thereafter until the reaction/<del>pain</del> is of moderate or less severity.</p> <p>Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.</p> <p>Injection-site reactions (<u>injection site erythema, induration, ecchymosis, and pain</u>) will also be recorded as adverse events <del>as described in Section 7.1.</del></p>			<p>If a patient has severe injection site induration, erythema, ecchymosis, or pain at 1 hour after completion of IMP administration, the patient will be reassessed at 3 hours after completion of IMP administration and hourly thereafter until the reaction is of moderate or less severity.</p> <p>Appropriate treatment may be provided if necessary, in which case it must be recorded as concomitant medication.</p> <p>Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) will also be recorded as adverse events.</p>			
<b>Section 8.6, Ancillary Studies – Wearable Sensor Substudy</b>						
<p>At selected sites <del>in the US</del>, a subset of patients (n=45, approximately 15 patients from each treatment group) will be asked to wear a sensor monitoring system (digital wearable device) on the wrist to track sleep patterns and <del>physical movement</del>activity patterns. The objective of this substudy is to evaluate changes in sleep-wake parameters and changes in <del>physical movement</del>activity as they relate to the occurrence of CH attacks. These changes will be evaluated during</p>			<p>At selected sites, a subset of patients (n=45, approximately 15 patients from each treatment group) will be asked to wear a sensor monitoring system (digital wearable device) on the wrist to track sleep patterns and activity patterns. The objective of this substudy is to evaluate changes in sleep-wake parameters and changes in activity as they relate to the occurrence of CH attacks. These changes will</p>			<p>Changed to align with how the Phillips device reports activity.</p>

Original text with changes shown	New wording	Reason/Justification for change
<p>days when patients experience CH attacks relative to days free of attacks and will be evaluated for use as predictors of seasonal onset of new CH epoch. The relationship between sleep-wake parameters, <del>physical movement</del> <u>activity levels</u>, and the frequency, intensity, and duration of CH attacks will also be determined.</p> <p>...</p> <p>The data will be used to assess whether changes in patterns of sleep and/or <del>physical movement</del> <u>activity</u> as captured by the digital wearable device can be used for early prediction and possible intervention of CH attacks. It is anticipated that risks to patients beyond those listed in Section 1.3 are unlikely.</p>	<p>be evaluated during days when patients experience CH attacks relative to days free of attacks and will be evaluated for use as predictors of seasonal onset of new CH epoch. The relationship between sleep-wake parameters, activity levels, and the frequency, intensity, and duration of CH attacks will also be determined.</p> <p>...</p> <p>The data will be used to assess whether changes in patterns of sleep and/or activity as captured by the digital wearable device can be used for early prediction and possible intervention of CH attacks. It is anticipated that risks to patients beyond those listed in Section 1.3 are unlikely.</p>	
<b>Section 9.1, Sample Size and Power Considerations</b>		
<p>A sample size of <del>258</del><sup>171</sup> patients (<del>86</del><sup>57</sup> evaluable patients completing the study per treatment group) will provide at least 90% power to detect a treatment difference of 4 CH attacks in the monthly average (assuming a common standard deviation [SD] of 8 CH attacks) at a 2-sided alpha level of <del>0.05</del><sup>30%</sup> in the proportion of patients (30% in placebo group and 60% in each of active treatment groups) with <del>≥50%</del> reduction at a 1-sided alpha level of 0.025. Assuming a <del>14</del><sup>20%</sup> discontinuation rate, <del>300</del><sup>216</sup> patients will be randomized in the trial.</p>	<p>A sample size of 258 patients (86 evaluable patients completing the study per treatment group) will provide at least 90% power to detect a treatment difference of 4 CH attacks in the monthly average (assuming a common standard deviation [SD] of 8 CH attacks) at a 2-sided alpha level of 0.05. Assuming a 14% discontinuation rate, 300 patients will be randomized in the trial.</p>	<p>The sample size was increased based on the new primary endpoint and decision not to re-estimate the sample size as part of the interim analysis.</p>
<b>Section 9.2.4, Per-Protocol Analysis Set</b>		
<p>The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any <del>major</del><sup>important</sup> protocol <del>violations</del><sup>deviations</sup>.</p>	<p>The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any important protocol deviations.</p>	<p>Change to terminology (violation to deviation) to align with guidance from the ICH.</p>

Original text with changes shown	New wording	Reason/Justification for change
Major <del>Important</del> protocol <del>deviations</del> <del>violations</del> will be determined before unblinding/database lock.	Important protocol deviations will be determined before unblinding/database lock.	
<b>Section 9.3.1, Handling Withdrawals and Missing Data</b>		
<u>Efficacy variables from patients who do not have diary data completed for the entire study period will be imputed.</u> For the <del>primary analysis</del> <del>analyses based on the proportion of responders</del> , patients who are terminated from the study early will considered as nonresponders. For patients who complete the study and have intermittent missing days in the e-diary, data will be prorated to 7 days. Details will be provided in statistical analysis plan.	Efficacy variables from patients who do not have diary data completed for the entire study period will be imputed. For the analyses based on the proportion of responders, patients who are terminated from the study early will considered as nonresponders. For patients who complete the study and have intermittent missing days in the e-diary, data will be prorated to 7 days. Details will be provided in statistical analysis plan.	Added to clarify that imputation will be used.
<b>Section 9.5.4.1, Primary Efficacy Analysis</b>		
The primary efficacy endpoint, <u>the mean change from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after administration of the first dose of the IMP;</u> <del>the proportion of patients with ≥50% reduction from baseline (run in period) in the monthly average number of CH attacks during the 12-week period after administration of the first dose of IMP,</del> will be analyzed using <u>an analysis of covariance (ANCOVA)</u> <del>Cochran Mantel Haenszel test stratified by baseline preventive medication use (yes/no).</del> The model will include treatment, baseline number of CH attacks, baseline preventive medication use (yes or no), gender, and region (US or other).	The primary efficacy endpoint the mean change from baseline (run-in period) in the monthly average number of CH attacks during the 12-week period after administration of the first dose of the IMP, will be analyzed using an analysis of covariance (ANCOVA). The model will include treatment, baseline number of CH attacks, baseline preventive medication use (yes or no), gender, and region (US or other).	Update made due to new primary endpoint.
<b>Section 9.5.4.3, Secondary and Exploratory Efficacy Analysis</b>		
The continuous endpoints will be analyzed using an ANCOVA or a mixed model for repeated measures <del>(MMRM)</del> . For the proportion of responders, defined	The continuous endpoints will be analyzed using an ANCOVA or a mixed model for repeated measures. For the proportion of	Update made due to new primary endpoint.

Original text with changes shown	New wording	Reason/Justification for change
as 50% or more reduction from baseline in the monthly average number of CH attacks, data will be analyzed <u>using a Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no)</u> <del>in a manner analogous to the primary endpoint.</del>	responders, defined as 50% or more reduction from baseline in the monthly average number of CH attacks, data will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline preventive medication use (yes/no).	
<b>Section 9.15, Planned Interim Analysis</b>		
An interim analysis for futility <del>and sample size re-estimation</del> will be performed once 50% of patients have completed 4-week assessments during the double-blind study period.	An interim analysis for futility will be performed once 50% of patients have completed 4-week assessments during the double-blind study period.	Sample size re-estimation will no longer be performed.
<b>Section 10, Quality Control and Quality Assurance (other section affected by this change: Appendix C, Quality Control and Quality Assurance)</b>		
This includes information about protocol amendments, deviations <del>and violations</del> , responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.	This includes information about protocol amendments, deviations, responsibilities of the investigator to study personnel, study monitoring, and audit and inspection.	Removed violations to align with guidance on terminology from ICH.
<b>Appendix B, Study Procedures and Assessments by Visit</b>		
Edit in each instance of the following: <ul style="list-style-type: none"> <li>• <del>Complete the numeric rating scale (NRS-11) questionnaire. Note: this will be completed by the patient after receiving the electronic diary device at home and not during the investigational site visit.</del></li> </ul>		Removed the NRS scale to meet the definition of the IHS for CH attack.
Edit in each instance of the following: <ul style="list-style-type: none"> <li>• Obtain <del>a 14.5-mL</del> blood sample (6 mL each for serum and plasma and <del>2.5</del> mL for RNA) for biomarker analysis.</li> </ul>	Edit in each instance of the following: <ul style="list-style-type: none"> <li>• Obtain a 14.5-mL blood sample (6 mL each for serum and plasma and 2.5 mL for RNA) for biomarker analysis.</li> </ul>	The PAXGene RNA sample will be collected into the PAXGene RNA tube, which requires 2.5 mL of blood. The blood volume was updated from 6.5 mL to 2.5 mL to reflect this.
Visit 2, procedures before administration of the IMP	<ul style="list-style-type: none"> <li>• Obtain a 4-mL blood sample for</li> </ul>	With the exception of the blood sample

Original text with changes shown	New wording	Reason/Justification for change
<ul style="list-style-type: none"> <li>Obtain a 4-mL blood sample for pharmacokinetics analysis from <del>the</del>either arm <u>that will not be used for dosing with IMP.</u></li> </ul>	<p>pharmacokinetics analysis from either arm.</p>	<p>collected immediately before the end of the IMP infusion (must be collected from the arm that is not used for IMP infusion), blood samples for pharmacokinetics analysis may be collected from either arm.</p>
<p>Visit 2 (Week 0 [Day 0+3 Days]) After completing predose assessments, patients will be treated with IMP. Refer to Section 5.1.1.1 for details regarding IMP administration. <u>A blood sample for pharmacokinetics analysis will be collected immediately before the end of the IMP infusion from the arm that is not used for the IMP infusion.</u></p>	<p>Visit 2 (Week 0 [Day 0+3 Days]) After completing predose assessments, patients will be treated with IMP. Refer to Section 5.1.1.1 for details regarding IMP administration. A blood sample for pharmacokinetics analysis will be collected immediately before the end of the IMP infusion from the arm that is not used for the IMP infusion.</p>	<p>The blood sample collected immediately before the end of the IMP infusion must be collected from the arm that is not used for the IMP infusion.</p>
<p>Edit in each instance of the following:</p> <ul style="list-style-type: none"> <li>Obtain a 4-mL blood sample for pharmacokinetics analysis <u>from either arm.</u></li> </ul>	<ul style="list-style-type: none"> <li>Obtain a 4-mL blood sample for pharmacokinetics analysis from either arm.</li> </ul>	<p>With the exception of the blood sample collected immediately before the end of the IMP infusion (must be collected from the arm that is not used for IMP infusion), blood samples for pharmacokinetics analysis may be collected from either arm.</p>
<ul style="list-style-type: none"> <li>Complete <del>the visual analog scale for pain intensity (VAS PI) of the PPSI using the electronic diary device. Note: this will be completed by the patient at home, not during the investigational site visit.</del></li> </ul>	<ul style="list-style-type: none"> <li>Complete the PPSI.</li> </ul>	<p>To align with changes in Section 6.7.</p>
<p>Edit in each instance of the following:</p> <ul style="list-style-type: none"> <li>Perform local injection site assessment immediately and at 1 hour after completing IMP administration. Additional injection site assessments may be performed based on the</li> </ul>	<ul style="list-style-type: none"> <li>Perform local injection site assessment immediately and at 1 hour after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection</li> </ul>	<p>To align with changes in Section 7.11.</p>

<b>Original text with changes shown</b>	<b>New wording</b>	<b>Reason/Justification for change</b>
severity of any observed injection site reaction and/or injection site pain.	site reaction.	
Week 1 (Day 7) Patients will complete the PGIC scale and the PPSI ( <del>complete the VAS-PI and respond to question about change in pain intensity</del> ) at 1 week after receiving IMP using the electronic diary device.	Week 1 (Day 7) Patients will complete the PGIC scale and the PPSI at 1 week after receiving IMP using the electronic diary device.	To align with changes in Section 6.7.
Edit in each instance of the following: Complete the PPSI ( <del>complete the VAS-PI and respond to question about change in pain intensity</del> ).	Complete the PPSI.	To align with changes in Section 6.7.
<b>Appendix N, Pharmacokinetics Samples (other section affected by this change: Appendix O, Immunogenicity Samples)</b>		
Samples will be stored at a temperature of -70°C to <del>±</del> -20°C ( <u>inclusive</u> ) in an upright position until they are shipped to the central laboratory.	Samples will be stored at a temperature of -70°C to -20°C (inclusive) in an upright position until they are shipped to the central laboratory.	Pharmacokinetic and ADA samples can be stored in a -70°C to -20°C freezer at the clinical sites before shipping.
<b>Appendix P, Exploratory Biomarkers Samples</b>		
Blood samples (total of <del>14</del> 8.5 mL; 6 mL each for plasma and serum and <del>2</del> 6.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 2 for serum, plasma, and RNA biomarker measures.	Blood samples (total of 14.5 mL; 6 mL each for plasma and serum and 2.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 2 for serum, plasma, and RNA biomarker measures.	The PAXGene RNA sample will be collected into the PAXGene RNA tube, which requires 2.5 mL of blood. The blood volume was updated from 6.5 mL to 2.5 mL to reflect this.

ADA=antidrug antibody; ANCOVA=analysis of covariance; CCH=chronic cluster headache; CH=cluster headache; CRF=case report form; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; ECH=episodic cluster headache; EOT=end of treatment; ICH=International Council on Harmonisation; IHS=International Headache Society; IMP=investigational medicinal product; ITT=intent to treat; MMRM=mixed model for repeated measures; NRS=numeric pain rating scale; PGIC=Patient Global Impression of Change; PP=per protocol; PPSI=Patient Perceived Satisfactory Improvement; RNA=ribonucleic acid SD=standard deviation; VAS=visual analog scale; VAS-PI-visual analog scale for pain intensity.



### 16.3. Letter of Clarification 04 Dated 13 December 2016



#### LETTER OF CLARIFICATION 04

Study numbers: TV48125-CNS-30056/ TV48125-CNS-30057/ TV48125-CNS-30058

#### Clinical Study Protocols

<b>TV48125-CNS-30056 A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Episodic Cluster Headache</b>
IND number: 129606
EudraCT number: 2016-003278-42
Final Protocol Date:08/08/2016 Amendment #1 Approval 30 Nov 2016

<b>TV48125-CNS-30057 A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group Study Comparing the Efficacy and Safety of 2 Dose Regimens (Intravenous/Subcutaneous and Subcutaneous) of TEV-48125 versus Placebo for the Prevention of Chronic Cluster Headache</b>
IND number: 129606
EudraCT number: 2016-003171-21
Date: 08/08/2016 Amendment #1 Approval 30 Nov 2016

<b>TV48125-CNS-30058 A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety of TEV-48125 for the Prevention of Cluster Headache</b>
IND number: 129606
EudraCT number: 2016-003172-43
Date: 08/08/2016 Amendment #1 Approval 30 Nov 2016



December 13th, 2016

Dear Investigator

The purpose of this letter of clarification is to provide clarifications to Appendix E, G and H of the protocol. The following updates will be implemented in the event of a protocol amendment.

Current wording	Proposed wording	Rationale
<p><b>Appendix E: WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS</b> Women of childbearing potential are defined as:</p> <ul style="list-style-type: none"> <li>• <del>not</del>-surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile</li> <li>• 1 year postmenopausal (no menses for 12 months without alternative medical cause plus an increased concentration of follicle-stimulating hormone of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy</li> </ul>	<p><b>Appendix E: WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS</b> Women of non-childbearing potential are defined as:</p> <ul style="list-style-type: none"> <li>• surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile</li> <li>• 1 year postmenopausal (no menses for 12 months without alternative medical cause plus an increased concentration of follicle-stimulating hormone of more than 30 U/L) in women not using hormonal contraception or hormonal replacement therapy</li> </ul>	<ul style="list-style-type: none"> <li>• Correction of wording regarding childbearing potential</li> <li>• Lower range for postmenopausal FSH updated to 30 U/L. The range was adjusted to reflect that from the clinical point of view, women without menses for 12 months and FSH of 30 U/L should be considered postmenopausal</li> </ul>
<p><b>APPENDIX H: PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS</b></p> <p><b>Disallowed Concomitant Medications</b> Systemic steroids are not allowed during the double-blind treatment period of this long-term extension study. Note that intra-articular steroid injections, steroid ear drops, steroids for ocular use, and steroid creams for topical use are permitted during the study.</p>	<p><b>APPENDIX H: PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS</b></p> <p><b>Disallowed Concomitant Medications</b> Systemic steroids are not allowed during the double-blind treatment period of this long-term extension study. Note that <b>intranasal</b>, intra-articular steroid injections, steroid ear drops, steroids for ocular use, and steroid creams for topical use are permitted during the study.</p>	<ul style="list-style-type: none"> <li>• Clarifying that intranasal steroids are allowed, along with other non-systemic steroids, as these do not influence on the course of the cluster headaches. Systemic steroids or any steroids cycle to treat cluster headaches cycles are disallowed, as they can mask an improvement that might affect the trial observation and results.</li> </ul>
<p><b>APPENDIX G: HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL</b></p>	<p><b>APPENDIX G: HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL</b></p>	<ul style="list-style-type: none"> <li>• Updating equilibration time to syringes prior administration into IV bag (45-60 minutes)</li> </ul>



<p><b>PRODUCT(S)</b></p> <p>Preparation instructions for iv infusions: The contents of 4 prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) or 1.5 mL of placebo will be added to 500 mL of normal saline solution. The iv infusion will be administered over approximately 1 hour.</p> <p>Preparation instructions for sc injections: IMP should be allowed to equilibrate at room temperature for <b>15 to 30</b> minutes before sc administration. A 1.5 mL volume from each syringe in each visit kit(s) must be injected sc for dosing to be considered complete. Refer to Appendix U for additional details regarding recommended sc injection sites.</p>	<p><b>PRODUCT(S)</b></p> <p>Preparation instructions for iv infusions: <b>IMP syringes should be allowed to equilibrate at room temperature for 45 to 60 minutes before administration into the IV bag.</b> The contents of 4 prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) or 1.5 mL of placebo will be added to 500 mL of normal saline solution. The iv infusion will be administered over approximately 1 hour.</p> <p>Preparation instructions for sc injections: IMP should be allowed to equilibrate at room temperature for <b>45 to 60</b> minutes before sc administration. A 1.5 mL volume from each syringe in each visit kit(s) must be injected sc for dosing to be considered complete. Refer to Appendix U for additional details regarding recommended sc injection sites.</p>	<ul style="list-style-type: none"> <li>Updating the needed equilibration time of syringes prior to subcutaneous administration to 45-60 minutes. Due to the pre filled syringes volume, the time required for the IMP to reach room temperature is 45-60 min. It is important to reach room temperature in order to minimize the force required to expel the drug product from the pre filled syringes to enable the fluid to flow smoothly. Please note that there is no safety concern associated with the equilibration time.</li> </ul>
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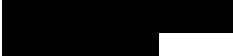
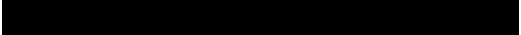

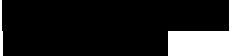


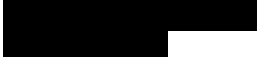



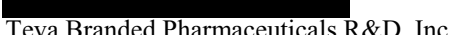



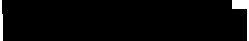
These clarifications are **not considered substantial** and will be incorporated to the protocol if an amendment will occur. Please ensure that this letter is maintained with the study protocol. Also, please provide a copy of this letter to your IRB/IEC for review and acknowledgement.

Please feel free to contact [redacted] if you have any questions or concerns regarding this letter.

Sincerely [redacted]  
 Signature [redacted]  
 Name: [redacted]

[redacted]  
 [redacted] Teva Pharmaceuticals

**APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS**

<b>Sponsor’s Authorized Representative</b>	  Teva Branded Pharmaceutical Products R&D, Inc. 
<b>Legal Representative of the Sponsor in the EU</b>	  Teva GmbH (after merger) Teva GmbH Graf-Arco-Str.3 89079 Ulm Germany 
<b>Sponsor’s Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study</b>	  Teva Branded Pharmaceutical Products R&D, Inc. 
<b>Sponsor’s Contact Point designated by the Sponsor for Further Information on the Study</b>	  Teva Branded Pharmaceuticals R&D, Inc.    Teva Branded Pharmaceuticals R&D, Inc. 



<b>Pharmacogenomics/Biomarker Evaluation</b>	[REDACTED] Teva Branded Pharmaceuticals R&D, Inc. [REDACTED]
<b>Electronic Clinical Outcome Assessment</b>	eResearch Technology, Inc. 1818 Market Street Philadelphia, PA 19103
<b>Web and Phone Integrated Interactive Response Technology</b>	Y-PRIME

## **APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT**

### **1. Procedures for Screening (Visit 1, 28 to 31 Days Before Visit 2)**

The screening visit (visit 1) will take place at during a run-in period lasting at least 4 weeks (+3 days) before visit 2 (week 0). The following procedures will be performed at visit 1:

- Obtain written informed consent before any other study-related procedures are performed. A subset of patients at selected sites in the US will also consent to participation in the wearable sensor biomarkers substudy.
- Review medical and psychiatric history.
- Review medication history.
- Record demographic and baseline characteristics.
- Review inclusion and exclusion criteria.
- Perform a physical examination, including height and weight. Body mass index will be calculated from the screening height and weight.
- Perform triplicate 12-lead ECGs.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Inquire about adverse events.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis). In case of abnormal coagulation during screening (run-in period) or if other specific urgent tests are required, a local retest can be authorized by the sponsor or designee on a case-by-case basis.
- Perform serum  $\beta$ -HCG pregnancy test (for women of childbearing potential only).
- Perform serum follicle-stimulating hormone test (postmenopausal women only).
- Record cluster headache (CH) attack information in the electronic diary device. Note: this will be completed by the patient at home, not during the investigational site visit.
- Complete the eC-SSRS Baseline/Screening version.

Patients who meet inclusion and none of the exclusion criteria will be given an electronic diary device and trained on its use and compliance requirements. These patients will complete a run-in period lasting at least 4 weeks (+3 days) during which they will enter CH attack information daily.

### **2. Procedures Before Administration of Investigational Medicinal Product (Baseline [Visit 2, Day 0+3 day(s)])**

Patients who meet the inclusion and exclusion criteria at visit 1 will continue to visit 2 (week 0), when baseline assessments will be conducted.

The following procedures will be performed at visit 2 (week 0):

- Review inclusion/exclusion criteria.
- Review study compliance.
- Review electronic diary data including compliance.
- Perform triplicate 12-lead ECGs.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a physical examination (including weight).
- Inquire about adverse events.
- Inquire about concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform urine  $\beta$ -HCG pregnancy test (for women of childbearing potential only).
- Record CH attack information in the electronic diary device. Note: this will be completed by the patient at home, not during the investigational site visit.
- Obtain a 4-mL blood sample for pharmacokinetics analysis from either arm.
- Obtain a 5-mL blood sample for ADA analysis.
- Obtain a 6-mL blood sample for pharmacogenomics analysis.
- Obtain blood sample for biomarker analysis (8.5-mL serum, 6 mL plasma, and 2.5 mL for ribonucleic acid [RNA]).
- Obtain a 5-mL urine sample for biomarker analysis.
- Administer the HADS, EQ-5D questionnaire, SF-12, and WPAI questionnaire.
- Each patient's partner/family member completes the Impact on Partner and Family questionnaire. Partners/family members will be asked to attend the study visit with the patient. Partners/family members will be asked to attend the study visit with the patient or to return to the investigational center within  $\pm 3$  days of the patient's visit if unable to appear at the same time.
- Complete the PPSI.
- Complete the eC-SSRS Since Last Visit version.

Patients who meet eligibility criteria will be randomized to 1 of the treatment groups.

Eligible patients who consented to participate in the wearable sensor substudy, who are able to demonstrate appropriate use of the wearable device, and who are willing to comply with the requirements for use of the digital wearable device will be given the wearable device and accessories. The device will be worn on the wrist throughout the 12-week double-blind treatment period.



### **3. Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period [Visit(s) 2 through 5, Day(s) 0 through 84+3 day(s)])**

Eligible patients will complete entries of CH attack information (ie, occurrence, number of attacks, and duration of attacks) using electronic diary devices daily from visit 2 through visit 5 (week 12). See Section 6.1 for additional details.

#### **Visit 2 (Week 0 [Day 0+3 Days])**

After completing predose assessments, patients will be treated with IMP. Refer to Section 5.1.1 for details regarding IMP administration. A 4-mL blood sample for pharmacokinetics analysis will be collected at the end of the IMP infusion (+10 minutes) from the arm that is not used for the IMP infusion.

The following procedures and assessments will be performed at visit 2 (week 0) after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour ( $\pm 15$  min) after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection site reaction. See Section 7.11 for additional details.
- Evaluate for anaphylaxis and hypersensitivity reaction.
- Inquire about postdose adverse events before the patient leaves the study center.

#### **Week 1 (Day 7)**

Patients will complete the PGIC scale and the PPSI at 1 week after receiving IMP using the electronic diary device.

#### **Visit 3 (Week 4 [Day 28+3 Days])**

The following predose procedures and assessments will be performed at visit 3:

- Review study compliance.
- Review electronic diary data.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Inquire about adverse events.
- Inquire about concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform urine  $\beta$ -HCG pregnancy test (for women of childbearing potential only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis from either arm.
- Obtain a 5-mL blood sample for ADA analysis.
- Administer the HADS, EQ-5D questionnaire, SF-12, and WPAI questionnaire.

- Each patient’s partner/family member completes the Impact on Partner and Family questionnaire. Partners/family members will be asked to attend the study visit with the patient. Partners/family members will be asked to attend the study visit with the patient or to return to the investigational center within  $\pm 3$  days of the patient’s visit if unable to appear at the same time.
- Complete the PPSI.
- Complete the PGIC scale.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

In addition, a 6-mL blood sample for pharmacogenomic analysis (DNA) may be obtained at this visit if the sample is not obtained at visit 2 (week 0), unless the patient declines or local regulations prohibit pharmacogenomic testing.

After completing predose assessments, patients will be treated with IMP. Refer to Section 5.1.1.1 for details regarding IMP administration.

The following procedures and assessments will be performed at visit 3 (week 4) after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour ( $\pm 15$  min) after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection site reaction. See Section 7.11 for additional details.
- Evaluate for anaphylaxis and hypersensitivity reactions.
- Inquire about postdose adverse events before the patient leaves the study center.

#### **Visit 4 (Week 8 [Day 56+3 Days])**

The following predose procedures and assessments will be performed at visit 4:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Inquire about adverse events.
- Inquire about concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform urine  $\beta$ -HCG pregnancy test (for women of childbearing potential only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis from either arm.
- Complete the PPSI.
- Complete the PGIC scale.

- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

In addition, a 6-mL blood sample for pharmacogenomic analysis (DNA) may be obtained at this visit if the sample is not obtained at an earlier visit, unless the patient declines or local regulations prohibit pharmacogenomic testing.

After completing predose assessments, patients will be treated with IMP. Refer to Section 5.1.1.1 for details regarding IMP administration.

The following procedures and assessments will be performed at visit 4 (week 8) after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour ( $\pm 15$  min) after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection site reaction. See Section 7.11 for additional details.
- Evaluate for anaphylaxis and hypersensitivity reactions.
- Inquire about postdose adverse events before the patient leaves the study center.

#### **End-of-Treatment Visit (Visit 5 [Week 12 (Day 84+3 Days)]/Early Withdrawal Visit**

The following procedures and assessments will be performed at the EOT visit (visit 5)/early withdrawal visit:

- Review electronic diary data
- Review study compliance.
- Perform triplicate 12-lead ECGs.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a physical examination (including weight).
- Inquire about adverse events.
- Inquire about concomitant medications.
- Perform clinical laboratory tests (serum chemistry, hematology, coagulation, and urinalysis).
- Perform a serum  $\beta$ -HCG pregnancy test (for women of childbearing potential only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis from either arm.
- Obtain a 5-mL blood sample for ADA analysis.
- Obtain blood sample for biomarker analysis (8.5-mL serum, 6 mL plasma, and 2.5 mL for ribonucleic acid [RNA]).
- Obtain a 5-mL urine sample for biomarker analysis.
- Administer the HADS, EQ-5D questionnaire, SF-12, and WPAI questionnaire.

- Each patient’s partner/family member completes the Impact on Partner and Family questionnaire. Partners/family members will be asked to attend the study visit with the patient. Partners/family members will be asked to attend the study visit with the patient or to return to the investigational center within  $\pm 3$  days of the patient’s visit if unable to appear at the same time.
- Complete the PPSI.
- Complete the PGIC scale.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

In addition, a 6-mL blood sample for pharmacogenomic analysis (DNA) will be obtained at this visit if the sample is not obtained at an earlier visit, unless the patient declines or local regulations prohibit pharmacogenomic testing.

Patients enrolling into Study TV48125-CNS-30058 for the purpose of evaluating the long-term safety of fremanezumab on the same day as this visit will keep the electronic diary device. All other patients will return the electronic diary device after completing this visit.

Patients in the wearable device substudy will return the wearable sensor if they do not rollover into the long-term safety study (Study TV-48125-CNS-30058) or if they rollover into the long-term safety study but do not wish to continue participating in the wearable sensor substudy.

#### **4. Unscheduled Visits**

An unscheduled visit may be performed at any time during the study at the patient’s request and as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the CRF as well as any other data obtained from procedures and assessments.

Procedures performed during unscheduled visits include:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (including systolic and diastolic blood pressure, pulse, and body temperature).
- Inquire about adverse events.
- Inquire about/review concomitant medications.
- Complete the eC-SSRS Since Last Visit version.

Other procedures may be performed at the discretion of the investigator.

## **APPENDIX C. QUALITY CONTROL AND QUALITY ASSURANCE**

### **Protocol Amendments and Protocol Deviations**

#### **Protocol Amendments**

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IEC/IRB and national and local competent authorities, as applicable, except when necessary to address immediate safety concerns to the patients or when the change involves only nonsubstantial logistics or administration. The principal investigator at each investigational center, the coordinating investigator (if applicable), and the sponsor will sign the protocol amendment.

#### **Protocol Deviations**

Any deviation from the protocol that affects, to a significant degree, (a) the safety, physical, or mental integrity of the patients in the study and/or (b) the scientific value of the study will be considered an important protocol deviation. Important protocol deviations may include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion and exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to IMP administration; use of prohibited medications. All important protocol deviations will be reported to the responsible IEC/IRB, as required.

When an important protocol deviation is reported, the sponsor will determine whether to discontinue the patient from the study or permit the patient to continue in the study, with documented approval from the medical expert. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study. A noncompliant patient may continue taking the study treatment only if this does not jeopardize the patient's safety. The sponsor will assess each protocol deviation and decide whether any of these noncompliances should be reported to the Regulatory Authority as a serious breach of GCP and the protocol.

Changes in the inclusion and exclusion criteria of the protocol are **not** prospectively granted by the sponsor. If investigational center personnel learn that a patient who did not meet protocol inclusion and exclusion criteria was entered in a study, they must immediately inform the sponsor of the protocol deviation. A deviation from the eligibility criteria will always result in study drug discontinuation in case the patient has not been dosed. In case a patient who was wrongly randomized has already started taking the study drug, a risk/benefit evaluation has to take place and a strong clinical justification must be provided in case the patient is not withdrawn from the study drug. If such patient has already completed the study or has withdrawn early, no action will be taken but the deviation will be recorded.

#### **Information to Study Personnel**

The investigator is responsible for giving information about the study to all personnel members involved in the study or in any element of patient management, both before starting the study and during the course of the study (eg, when new personnel become involved). The investigator must ensure that all study personnel are qualified by education, experience, and training to perform their specific task. These study personnel members must be listed on the investigational center

authorization form, which includes a clear description of each personnel member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study personnel, including the investigator, and for ensuring they comply with the protocol.

### **Study Monitoring**

To ensure compliance with GCP guidelines, the study monitor or representative is responsible for ensuring that patients have signed the informed consent form and the study is conducted according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines.

The study monitor is the primary association between the sponsor and the investigator. The main responsibilities of the study monitor(s) are to visit the investigator before, during, and after the study to ensure adherence to the protocol, that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and when changes to the consent form are warranted, in accordance with IEC/IRB approvals.

The study monitors will contact the investigator and visit the investigational center according to the monitoring plan. The study monitor will be permitted to review and verify the various records (CRFs and other pertinent source data records, including specific electronic source document relating to the study) to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of study progress, other sponsor personnel may, on request, accompany the study monitor on visits to the investigational center. The investigator and assisting personnel must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected during the course of these monitoring visits or provided in follow-up written communication.

### **Audit and Inspection**

The sponsor may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCP guidelines, and applicable regulatory requirements. The sponsor's Global Clinical Quality Assurance, independent of Global Specialty Development, is responsible for determining the need for (and timing of) an investigational center audit.

The investigator must accept that competent authorities and sponsor representatives may conduct inspections and audits to verify compliance with GCP guidelines.

## **APPENDIX D. ETHICS**

### **Informed Consent**

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study, including the written information approved by the IEC/IRB. All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

Written informed consent will be obtained from each patient before any study specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in the informed consent form, which will be signed and personally dated by the patient and by the person who conducted the informed consent discussion. The investigator will keep the original informed consent forms, and copies will be given to the patients. It will also be explained to the patients that the patient is free to refuse participation in the study and free to withdraw from the study at any time without prejudice to future treatment.

### **Competent Authorities and Independent Ethics Committees/Institutional Review Boards**

Before this study starts, the protocol will be submitted to the national competent authority and to the respective IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and competent authority (as applicable) for the investigational center give written approval or a favorable opinion.

### **Confidentiality Regarding Study Patients**

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, patients will be identified not by their names, but by an identification number.

Personal medical information may be reviewed for the purpose of patient safety or for verifying data in the source and the CRF. This review may be conducted by the study monitor, properly authorized persons on behalf of the sponsor, Global Quality Assurance (GCA), or competent authorities. Personal medical information will always be treated as confidential.

### **Registration of the Clinical Study**

In compliance with national and local regulations and in accordance with Teva standard procedures, this clinical study will be registered on trials registry websites.

## **APPENDIX E. WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS**

Assessment of likelihood of possible interaction between investigational medicinal product (IMP) or concomitant medications and hormonal contraception should be conducted. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

Drug interaction studies have not been conducted with fremanezumab. Like other therapeutic antibodies, fremanezumab is expected to be primarily metabolized via proteolytic catabolism. Therefore, interaction with and impact on drug metabolizing enzymes (eg, CYP isoforms) is considered unlikely in humans.

In addition, fremanezumab is not expected to indirectly influence the CYP enzymes. In general, protein products that are cytokine modulators have been reported to affect the metabolism or disposition of co-administered medication by altering CYP enzymes/transporters (FDA 2012). Fremanezumab is an IgG2 isotype that is directed against a non-immunologic and soluble (not cell bound) target. Thus, the risk of cytokine release is considered to be low in the clinical setting. Furthermore, fremanezumab was tested for stimulation of pro-inflammatory cytokine release in human whole blood (Study 111320). Fremanezumab did not elicit significant cytokine release (TNF- $\alpha$ , IL-6, INF- $\gamma$ , or IL-1 $\beta$ ) in any donor including at concentrations up to 100  $\mu\text{g/mL}$ . As such, there is no reason to suspect that fremanezumab may influence CYP activity.

### **Women of non-childbearing potential are defined as:**

- Surgically (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- One year postmenopausal (stable amenorrhea for 12 months without alternative medical cause plus high follicle-stimulating hormone (FSH) in the postmenopausal range) in women not using hormonal contraception or hormonal replacement therapy
- Women in stable post-menopause, but are taking hormone replacement therapy for the treatment of menopausal symptoms, may be considered eligible for the study even with the lower serum FSH. They do not need to use other contraception.

### **Highly effective birth control methods:**

Highly effective birth control methods are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered. Such methods include the following:

- Combined estrogen and progestogen hormonal contraception (oral, intravaginal, or transdermal) associated with inhibition of ovulation; these should be initiated at least 7 days before dosing of IMP.
- Progestogen-only hormonal contraception (oral, injectable, or implantable) associated with inhibition of ovulation; these should be initiated at least 7 days before dosing of IMP.



- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS) need to be in place at least 2 months before screening.
- Bilateral tubal occlusion
- Vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.
- Sexual abstinence is only considered a highly effective method if defined as refraining from heterosexual intercourse in the defined period. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.
- Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods of contraception (according to Medicines and Healthcare Products Regulatory Agency).

**Acceptable birth control methods:**

Acceptable birth control methods that result in a failure rate of more than 1% per year include progestogen-only oral hormonal contraception for which the inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide; cap; diaphragm; or sponge with spermicide. The combinations of male condom with cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable but not highly effective methods of birth control.

**Unacceptable birth control methods:**

Periodic abstinence (calendar, symptothermal, or post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

**Male contraception:**

Male subjects must always use a condom.

**Vasectomy:**

Use of contraceptive methods applies also to vasectomized men.

**Pregnant female partners of male study participants:**

Male study participants must use condoms during intercourse if their female partners are pregnant.

## **APPENDIX F. LOST TO FOLLOW-UP**

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and if the site is unable to establish contact with the patient after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

## **APPENDIX G. HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL PRODUCT(S)**

### **Preparation of Investigational Medicinal Products**

Fremanezumab or placebo will be provided in prefilled syringes contained in uniquely numbered kits and stored accordingly (see above). At the time of each study visit, the IRT will be queried, and investigational site personnel will retrieve the appropriately numbered kit(s). Kit numbers will be entered into the CRF.

Preparation instructions for iv infusions: Investigational medicinal product (IMP) syringes should be allowed to equilibrate at room temperature for 45 to 60 minutes before administration into the iv bag. The contents of 4 prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) or 1.5 mL of placebo, will be added to 500 mL of normal saline solution. The iv infusion will be administered over approximately 1 hour.

Preparation instructions for sc injections: IMP should be allowed to equilibrate at room temperature for 45 to 60 minutes before sc administration. A 1.5 mL volume from each syringe in each visit kit(s) must be injected sc for dosing to be considered complete. Refer to [Appendix U](#) for additional details regarding recommended sc injection sites.

### **Storage and Security**

The investigator or designee must confirm appropriate temperature conditions have been maintained for all IMPs received and any discrepancies are reported and resolved before use of the IMPs.

The test IMP (fremanezumab) and placebo IMP must be stored refrigerated at 2°C to 8°C (36°F to 46°F), protected from light; the investigational site should have a process for monitoring the drug storage temperature.

Diversions are considered to have occurred when the legal supply chain of prescription analgesic medicinal products is broken, and medicinal products are transferred from a licit to an illicit channel of distribution or use.

### **Labeling**

Supplies of IMPs will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

### **Accountability**

Each IMP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The investigator is responsible for ensuring that deliveries of IMPs and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in

accordance with the CFR or national and local regulations, and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs and only authorized staff at the investigational center may supply or administer IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized staff at the investigational center.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

A record of IMP accountability (ie, IMP and other study materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. Empty and partially used prefilled syringes should be destroyed, and the investigational site should provide a certificate of destruction. If the investigational site does not have the capability to destroy the used and partially used prefilled syringes, the prefilled syringes should be sent back to the sponsor. Unused prefilled syringes of IMP will be returned to the sponsor or designee.

## **APPENDIX H. PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS**

### **1. Medications Commonly Prescribed for Cluster Headache**

The following medications will be considered as being used for the prevention of cluster headaches, regardless of the initial indication.

- verapamil
- lithium
- methysergide
- valproate
- topiramate

Patients are allowed to take up to 2 of these medications provided that they are on a stable dose and regimen for at least 2 weeks prior to screening and throughout the study.

Botox will not be a stable concomitant preventive medication for cluster headaches. If the patients were treated with Botox for the prevention of migraine, they should have had at least 2 cycles of Botox within 10 days of a new cluster cycle prior to screening.

### **2. Concomitant Medications Allowed and Disallowed**

#### Steroids:

Screening/run-in period and throughout the study: Systemic steroids are not allowed to be used in the treatment of cluster cycles during the screening/run-in period and for the duration of the study.

The only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use.

Screening/run-in period: Disallowed if patient used systemic steroids to treat the current CH cycle or for any other indication to treat the current CH cycle within  $\leq 7$  days of screening.

#### Butalbital:

Screening/run-in period: Disallowed if used more than 10 days during the screening/run-in period. Patients can use butalbital as needed (PRN) after randomization into the study.

#### Opioids:

Screening/run-in period: Disallowed if used more than 15 days during the screening/run-in period. Patients can use opioids PRN after randomization into the study.

## **APPENDIX I. ICHD 3-BETA DIAGNOSTIC CRITERIA**

Refer to the ICHD 3-Beta Diagnostic Criteria ([Headache Classification Committee of the IHS 2013](#)) for additional details.

### **3.1 Cluster headache**

*Diagnostic criteria:*

- A) at least 5 attacks fulfilling criteria B-D
- B) severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15 to 180 minutes (when untreated)<sup>1</sup>
- C) either or both of the following:
  - 1) at least 1 of the following symptoms signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhea
    - c) eyelid edema
    - d) forehead and facial sweating
    - e) forehead and facial flushing
    - f) sensation of fullness in the ear
    - g) miosis and/or ptosis
  - 2) a sense of restlessness or agitation
- D) attacks have a frequency of between 1 every other day and 8 per day for more than half of the time when the disorder is active
- E) not better accounted for by another ICHD 3-beta diagnosis

#### **3.1.1 Episodic cluster headache**

*Diagnostic criteria:*

- A) attacks fulfilling criteria for 3.1 Cluster headache and occurring in bouts (cluster period)
- B) at least 2 cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of  $\geq 1$  month

#### **3.1.2 Chronic cluster headache**

*Diagnostic criteria:*

- A) Attacks fulfilling criteria for 3.1 Cluster headache and criterion B
- B) Occurring without a remission period or with remissions lasting  $< 1$  month, for  $\geq 1$  year

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<sup>1</sup> During part (but less than half) of the time course of 3.1 Cluster headache, attacks may be less severe and/or of shorter or longer duration.

## **APPENDIX J. GUIDANCE ON SAFETY MONITORING**

### **Guidance on Monitoring Patients with Elevated Liver Function Tests**

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

In any case of elevated ALT or AST to a level exceeding  $\geq 2 \times$  the ULN (including patients whose baseline ALT or AST levels are  $\geq 2 \times$  and  $\leq 3 \times$  the ULN, who may be enrolled in the study), a thorough medical history and physical examination with a focus on liver disease should be undertaken.<sup>2</sup> In addition, the patient should be instructed to refrain from alcoholic beverages.

In case of symptoms compatible with drug-induced liver injury during the study, patients will be instructed to return to the study center for an unscheduled visit or to go to the emergency room to measure liver enzymes as soon as possible. Solitary elevations of total, direct, or indirect bilirubin, not accompanied by elevations of ALT or AST should be managed according to the discretion of the treating physician.

#### **Elevation of Either ALT or AST to $\geq 3 \times$ ULN**

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

- The day in which the abnormal value is received from the laboratory will be considered as day 0.
- The investigator should repeat the test for confirmation purposes (this may be performed in a local laboratory along with complete blood cell [CBC] count and differential to assess for eosinophilia; in general, in case a blood sample is sent to a local laboratory, the following assessments [and reference ranges] are mandatory: ALT [serum glutamic pyruvic transaminase], AST [serum glutamic oxaloacetic transaminase], ALP, bilirubin [total, direct, and indirect], CBC [with differential for eosinophil count, separate tube], and INR [separate tube; not to be sent in a confirmatory test]). The investigator should also question the patient regarding symptoms.

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

- the baseline value was within the normal range and ALT or AST is still  $\geq 3 \times$  the ULN
- the baseline value was above the ULN and ALT or AST is  $\geq 2 \times$  the baseline value

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<sup>2</sup> 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 investigator. Physical examination, including signs of chronic liver disease.

**Additional Tests/Evaluations:**

Upon confirmation of the abnormality as noted above, the following additional evaluations should be performed and results should be recorded in the CRF:

- serology for hepatitis A (antibody and immunoglobulins M and G), B (core antibody total, core immunoglobulin M, and surface antigen), and C viruses (central laboratory)
- serology for autoimmune hepatitis: anti-nuclear antibodies (titer), anti-smooth muscle antibodies, and anti-liver kidney microsomal antibodies (central laboratory); further testing may be required in case of a positive result for hepatitis B or C
- ultrasound examination of the liver and biliary tract at the investigator's discretion
- other diagnostic tests/consultations as deemed necessary by the investigator (eg, serology for hepatitis E virus in case of travel to endemic geography)
- observation and follow-up (to be performed after the abnormality was confirmed as above)

**ALT or AST  $\geq 3 \times$  ( $>3.5 \times$  the ULN if the Baseline Value is  $>2.5 \times$  the ULN) but  $<5 \times$  the ULN**

In addition to the above procedures required for any elevation to levels  $>3 \times$  the ULN:

- Alanine aminotransferase, AST, GGT, ALP, total bilirubin, direct bilirubin, indirect bilirubin, CBC and differential (to assess for eosinophilia), and INR should be monitored on days 5 ( $\pm 2$  days), 8 ( $\pm 2$  days), 14 ( $\pm 3$  days), and 28 ( $\pm 3$  days). On at least 1 of these days, the test should be performed centrally. (The INR should be sent to a local laboratory only.)
- In cases where a local laboratory is used, the results should be recorded in the CRF, accompanied by the reference range of the relevant measurements.
- Should the abnormality ( $\geq 3 \times$  the ULN in case baseline was within the normal range or  $\geq 2 \times$  the ULN in case the baseline value was above ULN but still  $<5 \times$  the ULN) persist further, the patient will be followed according to the investigator's discretion, but a blood sample for ALT, AST, GGT, ALP, and total bilirubin, direct bilirubin, indirect bilirubin should be sent to the central laboratory at least once a month.

**ALT or AST  $\geq 5 \times$  but  $<8 \times$  the ULN**

In addition to the above procedures required for any elevation to levels  $>3 \times$  the ULN:

- Alanine aminotransferase, AST, GGT, ALP, total bilirubin, direct bilirubin, indirect bilirubin, CBC and differential count (to assess for eosinophilia), and INR should be monitored twice a week.
- At least for every other measurement, the tests should be sent to the central laboratory. The rest of the tests may be sent to a local laboratory. The INR should always be sent to a local laboratory.



**ALT or AST  $\geq 8 \times$  the ULN**

In addition to the above procedures required for any elevation to levels  $>3 \times$  the ULN:

- The IMP should be discontinued immediately, and the early withdrawal visit should be performed.
- For follow-up guidance, please see below section “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  $\geq 3 \times$  the ULN, combined with INR  $>1.5 \times$  the ULN or total bilirubin  $>2 \times$  the ULN
- any increase in ALT or AST to  $\geq 3 \times$  the ULN, which is accompanied by symptoms clearly associated with impaired liver function (eg, vomiting, nausea, fever, rash, and eosinophilia) and not deemed related to other diseases (eg, vomiting or nausea triggered by cluster headache)
- any increase in ALT or AST to levels  $\geq 5$  but  $<8 \times$  the ULN, which is persistent for  $\geq 2$  weeks of repeated measurements
- any increase in ALT or AST to levels  $\geq 8 \times$  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 investigational site to return the IMP. Early withdrawal visit activities should be performed as soon as possible.
- Liver enzymes should be monitored until normalization or stabilization of the abnormality, according to the discretion of the investigator.
- In any case, following the early withdrawal visit, the minimal follow-up period will be 30 days and will include measurement of liver enzymes at least once weekly (may be performed in local laboratory, with at least 1 test being sent to the central laboratory).
- Every effort should be made to complete the additional tests/evaluations, as described above.

## APPENDIX K. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

As detailed by [Sampson et al 2006](#), anaphylaxis is broadly defined as, “a serious allergic reaction that is rapid in onset and may cause death.” Diagnostic criteria defined by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network during the second symposium on the definition and management of anaphylaxis, modified from [Sampson et al 2006](#), are as follows:

Anaphylaxis is highly likely when any 1 of the following 3 criteria is 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 1 of the following:
  - a. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - b. reduced blood pressure 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 patient* (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 blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
  - d. persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to *known allergen for that patient* (minutes to several hours):
  - a. adults: systolic blood pressure of <90 mm Hg or >30% decrease from that person’s baseline

In the event of suspected anaphylaxis, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator. As a precaution, each investigational site should have a resuscitation cart nearby.

## APPENDIX L. TOTAL BLOOD VOLUME

The total blood volume to be collected for each patient in this study is approximately 131.5 mL (at maximum) for scheduled tests. An additional 30 mL of blood may be collected in the event of follow up for liver enzymes as detailed in [Appendix J](#).

### Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry	3.5	5	17.5
Serum pregnancy <sup>a</sup>	3.5	2	7
Hematology	2	5	10
Coagulation	4.5	5	22.5
FSH <sup>b</sup>	3.5	1	3.5
Pharmacokinetics	4	4	16
ADA <sup>c</sup>	5	3	15
Biomarker Serum	8.5	2	17
Biomarker Plasma	6	2	12
Biomarker RNA	2.5	2	5
Pharmacogenomic <sup>d</sup>	6	1	6
<b>Total</b>	--	<b>32</b>	<b>131.5</b>

<sup>a</sup> A serum pregnancy test will be performed for women of childbearing potential at screening only.

<sup>b</sup> Postmenopausal women only.

<sup>c</sup> ADA assessment will also be collected upon observation of severe hypersensitivity or anaphylaxis or if there is a suspected causal relationship of an adverse event potentially being related to immunogenicity (eg, lack of efficacy).

<sup>d</sup> Unless the patient declines testing or local regulations prohibit testing.

ADA=antidrug antibody; FSH=follicle-stimulating hormone; RNA=ribonucleic acid.

## APPENDIX M. CLINICAL LABORATORY TESTS

### Clinical Laboratory Tests

Serum Chemistry	Hematology and Coagulation	Urinalysis
Calcium	Hemoglobin	Color and appearance
Phosphate	Hematocrit	Protein
Sodium	Erythrocytes	Glucose
Potassium	Platelets	Albumin
Chloride	Leucocytes	Ketones
Magnesium	– Neutrophils	Leukocyte esterase
Creatinine	– Lymphocytes	Nitrite
Glucose	– Eosinophils	Bilirubin
Blood urea nitrogen (BUN)	– Monocytes	Hemoglobin
Alanine aminotransferase (ALT)	– Basophils	pH
Aspartate aminotransferase (AST)	Lymphocytes atypical	Specific gravity
Lactate dehydrogenase (LDH)	Prothrombin International Normalized Ratio (INR)	Microscopic tests
Gamma-glutamyl transpeptidase (GGT)		– Bacteria
Alkaline phosphatase		– Erythrocytes
Bicarbonate		– Leucocytes
Carbon dioxide		– Crystals
Protein		– Casts
Albumin		
Bilirubin		
Direct bilirubin		
Indirect bilirubin		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyltranspeptidase; INR=international normalized ratio; RBC=red blood cell; WBC=white blood cell.

## **APPENDIX N. PHARMACOKINETICS SAMPLES**

### **Specimen Sampling and Handling**

For plasma collection, samples will be collected in anticoagulant tubes, inverted slowly 6 to 8 times to mix the contents, and placed on water/ice (approximately 4°C). Blood samples will be centrifuged (1500 g, approximately 10 minutes, at 2 to 8°C) between 5 minutes and 1 hour after sampling. If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated plasma will be transferred in approximately equal portions in 2 labeled 2 mL-polypropylene tubes (Sets A and B).

Labels for samples should include study number, patient randomization number, nominal collection time (Visit number), Set A or B, and indication that they are pharmacokinetic samples. Samples will be stored at a temperature of –70°C to –20°C (inclusive) in an upright position until they are shipped to the central laboratory.

### **Shipment and Analysis of Samples**

Plasma samples for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis. Samples will be stored in an upright position at –70°C until assayed. The central laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped. An electronic file containing sample demographics will be emailed to the bioanalytical laboratory and the sponsor's representatives from bioanalytical departments for each shipment.

Set A samples will be transported frozen, with a temperature data logger and with dry ice sufficient for 4 days, on a monthly basis to the central laboratory. Central laboratory will ship the Set A samples on a monthly basis to the bioanalytical laboratory with dry ice sufficient for 4 days and with a temperature data logger.

Set B samples will be sent to the same laboratory as that for Set A. Instructions as to the disposition of the Set B samples will be provided by the sponsor. Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the sponsor's representatives of bioanalytical departments responsible for the bioanalysis while keeping the study blinding, if any, intact.

## **APPENDIX O. IMMUNOGENICITY SAMPLES**

### **Blood Sampling and Handling**

For serum collection, samples will be collected in Vacutainer tubes containing no anticoagulant, and allowed to set at room temperature for between 1 and 1.5 hours to allow for serum separation to occur. Samples will then be centrifuged (1500 g, approximately 10 minutes, at 2 to 8°C). If a refrigerated centrifuge is not available, samples should be chilled before centrifugation. Other measures should be taken as appropriate to prevent samples from heating significantly during centrifugation. Separated serum will be transferred in approximately equal portions in 2 labeled 2 mL-polypropylene tubes (Sets A and B).

Label of samples should include study number, patient randomization number, nominal collection time (Visit number), Set A or B, and indication that they are ADA samples. Serum samples will be stored at a temperature of –70°C to –20°C (inclusive) in an upright position until they are shipped to the central laboratory.

### **Shipment and Analysis of Samples**

Serum samples for all patients will be shipped from the investigational center to the central laboratory, where they will be stored until shipped to the sponsor or designee for analysis. Samples will be stored in an upright position at –70°C until analysis. The central laboratory will be notified before the shipment of the samples and will be sent the shipping information when the samples are shipped. An electronic file containing sample demographics will be emailed to the central laboratory for each shipment. The same will be copied to the sponsor's representatives of bioanalytical departments responsible for the bioanalysis.

Set A samples will be transported frozen, with a temperature data logger and with dry ice sufficient for 4 days, on a monthly basis to the central laboratory. Central laboratory will ship the set A samples on a monthly basis to the bioanalytical laboratory with dry ice sufficient for 4 days and with a temperature data logger.

Set B samples will be sent to the same laboratory as that for Set A. Instructions as to the disposition of the Set B samples will be provided by the sponsor. Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

Samples will be analyzed using an appropriate validated method. Timing of the initiation of sample analysis will be determined by the sponsor's representatives of bioanalytical departments responsible for the bioanalysis while keeping the study blinding, if any, intact.

## **APPENDIX P. EXPLORATORY BIOMARKERS SAMPLES**

Blood samples (8.5 mL serum, 6 mL plasma and 2.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in [Table 2](#) for serum, plasma, and RNA biomarker measures. Urine will be collected in parallel with blood collection. In addition, a 6-mL whole blood sample will be collected at baseline (or a later visit) for DNA. Details for processing and handling of each type of biomarker sample will be outlined in the laboratory manual.

All blood and urine tubes will be labeled with the patient code number. Following DNA extraction from the pharmacogenomic sample, the sample will be labeled with a new code (ie, double coding), so that genetic data will not be recorded with a patient number.

Samples will be stored for a period of up to 15 years from the last patient’s last visit in the main study and then destroyed.

### **Shipment and Analysis of Samples**

Biomarker samples for serum, plasma, RNA, and urine will be stored at  $-70^{\circ}\text{C}$  and sent to the central laboratory on dry ice, per instructions in the laboratory manual. Sample labels should include study number, patient randomization number, visit code, collection date and time, and indication that they are biomarker samples. Shipments should be made as specified in the laboratory manual. An electronic file containing sample demographics will be emailed to the respective biomarker laboratory and the sponsor’s biomarker representative for each shipment.

Following DNA extractions of whole blood, the samples will be stored at  $-70^{\circ}\text{C}$  and labeled with a new code (ie, double coding), so that genomic data will not be recorded with a patient number. Data will be kept confidential and stored separately.

The biomarker sample analyses will be performed if and when required. Since new techniques continue to be developed, the method and laboratory that will be recommended for the future biomarker analysis cannot be anticipated.

## APPENDIX Q. PHARMACOGENOMIC ASSESSMENTS

Blood samples (6 mL) for pharmacogenomic assessments will be collected from all patients in the study who signed the ICF for the pharmacogenomic assessments at the time point detailed in [Table 2](#). Pharmacogenomic assessment potentially includes the association of DNA variations in specific genes of interest with clinical responses to test IMP (eg, efficacy, pharmacokinetics, tolerability, and safety features or disease susceptibility and severity features). The current list of genes with polymorphisms associated with either calcitonin gene-related peptide target engagement or cluster headache mechanism of action includes *CALCA*, *CALCB*, *CALCRL*, *CRCP*, *RAMP*, *PRDM16*, *AJAP1*, *TSPAN2*, *MEF2D*, *TRPM8*, *TGFBR2*, *PHACTR1*, *FHL5*, *C7orf10*, *MMP16*, *ASTN2*, *LRP1*, *APOA1BP*, *TBC1D7*, *FUT9*, *STAT6*, *ATP5B*, and *MTHFR* ([Anttila et al 2013](#)). The final list of genes that might be investigated will be selected at a later stage before the analysis to allow updating with new scientific information. Genetic analysis could also include sequencing of the whole genome if required.

Pharmacogenomic assessment will be performed based on study results. Samples will be used only for investigations related to headache or response to test IMP or related IMPs.

Details on processes for collection and shipment of these samples can be found in the procedural manual.



## **APPENDIX R. PRODUCT COMPLAINTS**

### **Clinical Product Complaints**

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical IMP supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [REDACTED] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving an IMP, all relevant samples (eg, the remainder of the patient’s IMP supply) should be sent back to the sponsor for investigative testing whenever possible.

#### **1. Product Complaint Information Needed from the Investigational Center**

In the event that the product complaint form cannot be completed, the investigator will provide the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No

- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

## **2. Handling of Investigational Medicinal Product(s) at the Investigational Center(s)**

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the IMP.

If it is determined that the investigational center must return all IMP, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

## **3. Adverse Events or Serious Adverse Events Associated with a Product Complaint**

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.1.2 and Section 7.1.5, respectively).

## **4. Documenting a Product Complaint**

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

## **APPENDIX S. DATA MANAGEMENT AND RECORD KEEPING**

### **Direct Access to Source Data and Documents**

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

If data are processed from other institutions or by other means (eg, clinical laboratory, central image center, or electronic diary data) the results will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management).

The medical experts, study monitors, auditors, IEC/IRB, and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

### **Data Collection**

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a CDMS that meets the technical requirements described in 21CFR Part 11 (USA) and documents of other concerned competent authorities. Before using the CDMS, it will be fully validated and all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational center by appropriately designated and trained personnel, and CRFs must be completed for each patient who provided informed consent. Patient identity should not be discernible from the data provided on the CRF.

If data are processed from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary data, ePRO tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

## **Data Quality Control**

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day to day data management tasks for this study are delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source, and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous, or data that are missing, will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

## **Archiving of Case Report Forms and Source Documents**

### Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

### Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the IMPs
- copies of all correspondence with sponsor, the IEC/IRB, and any competent authority

The investigator will retain all records related to the study and any additional records required, as indicated by the protocol and according to applicable laws and regulations, until the CRO or sponsor notifies the institution in writing that records may be destroyed. If, after 25 years from study completion, or earlier in the case of the investigational center closing or going out of business, the investigator reasonably determines that study record retention has become unduly burdensome, and sponsor has not provided written notification of destruction, then the investigator may submit a written request to sponsor at least 60 days before any planned disposition of study records. After receipt of such request, the sponsor may make arrangements for appropriate archival or disposition, including requiring that the investigator deliver such records to the sponsor. The investigator shall notify the sponsor of any accidental loss or destruction of study records.

## **APPENDIX T. PUBLICATION POLICY**

All unpublished information given to the investigator by the sponsor shall not be published or disclosed to a third party without the prior written consent of the sponsor.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results: “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” ([www.ICMJE.org](http://www.ICMJE.org)). Publication of the results will occur in a timely manner according to applicable regulations. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigational center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements:

- substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- 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

The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

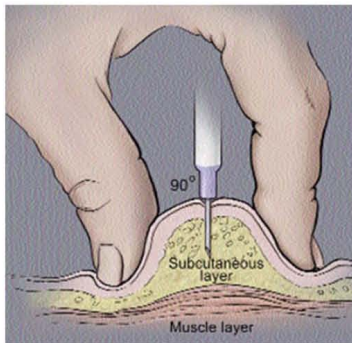
No patent applications based on the results of the study may be made by the investigator nor may assistance be given to any third party to make such an application without the written authorization of the sponsor.

## APPENDIX U. NATIONAL INSTITUTES OF HEALTH PATIENT EDUCATION GUIDELINES OF SEPTEMBER 2015

### NIH Clinical Center Patient Education Materials Giving a subcutaneous injection

#### What is a subcutaneous injection?

A subcutaneous injection is given in the fatty layer of tissue just under the skin.



A subcutaneous injection into the fatty layer of tissue (pinched up to give the injection) under the skin.  
Source: NIH Medical Arts

#### Why are subcutaneous injections given?

These injections are given because there is little blood flow to fatty tissue, and the injected medication is generally absorbed more slowly, sometimes over 24 hours. Some medications that can be injected subcutaneously are growth hormone, insulin, epinephrine, and other substances.

#### Preparing to give medication

Subcutaneous injections are not given if the skin is burned, hardened, inflamed, swollen, or damaged by a previous injection.

1. Wash your hands thoroughly. This is the best way to prevent infection.
2. Assemble your equipment:

##### Medication

May be a multidose vial of liquid or may be a vial with powder that requires “reconstitution.” Follow the manufacturer’s instructions as to what and how much diluent to use. The diluent is usually saline (a mixture of salt water) or sterile water

##### Syringe or pen and needle

Depending on the amount of medication to be given and the size of the child or adult:

- 0.5 cc, 1.0 cc, or 2 cc with 27-gauge needle (5/8 of an inch long)
- 3-cc luer lock syringe—used when solution is more than 1 cc
- 25-gauge needle (5/8 of an inch long) or 27-gauge needle (5/8 of an inch long)
- 0.3 mL insulin syringes with 31-gauge needles (3/16 to 5/16 inches long) are available for those who are visually impaired or for those who need very small doses of medication.
- medication log
- container for syringe disposal
- sterile 2 x 2-inch gauze pad
- alcohol pads

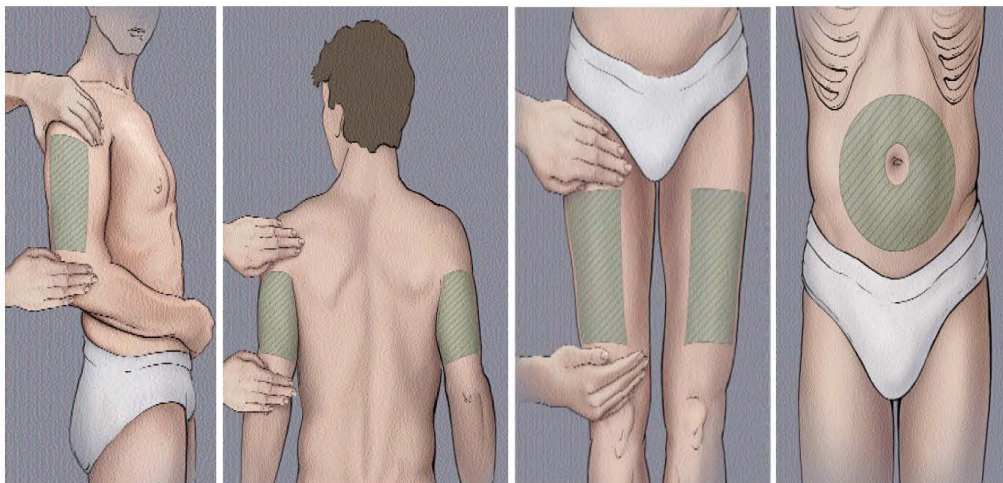
**Drawing up medication**

1. Check the label for correct medication.
2. Remove the soft metal or plastic cap protecting the rubber stopper of the vial.
3. If the medication vial or pen can be used for more than one dose, record the date and time on the label.
4. Clean the exposed rubber stopper using an alcohol swab.
5. Remove the syringe from the plastic or paper cover. If necessary, attach the needle securely.
6. Pull back and forth on the plunger by grasping the plunger handle. Grasping the handle end will prevent contamination of the plunger shaft (which is sterile).
7. With the needle capped, pull back the plunger, filling the syringe with air equal to the amount of medication to be administered.
8. Remove the cap covering the needle and set it on its side to prevent contamination. Be careful not to touch the needle. The inside of the cap and needle is sterile, and the needle will be covered again with this cap.

**Locating injection sites**

Subcutaneous injections can be given in the arms, legs, or abdomen. Your nurse or doctor will help you select the best sites to administer your medication.

- To locate injection sites on the arms, fold one arm across the chest. Place your hand on the shoulder and draw an imaginary line below your hand. Place another hand on the elbow. Draw an imaginary line down the outer side of the arm and down the center front of the arm, starting at the elbow. The area inside these imaginary lines is where injections are given. (If you are injecting imagine the hand placement).
- To locate injection sites on the thighs, sit down, place your hand above the knee, and draw an imaginary line above it. Place your hand at the uppermost part of the thigh and draw an imaginary line below your hand. Draw an imaginary line down the outer side of the leg and down the center front of the leg. The area within these imaginary lines is where injections may be given.
- To locate injection sites on the abdomen, place your hands on the lower ribs and draw an imaginary line between them. Use this area below your hands for injections, as far around as you can pinch up fatty tissue. Use a 1-inch area around the navel.



Source: NIH Medical Arts



9. With the vial in an up-right position, push the needle through the cleansed rubber stopper on the vial. Push the needle in at a 90 degree angle, being careful not to bend the needle.
10. Inject the air in the syringe into the vial. Air is injected into a multi-dose vial to prevent a vacuum from forming. If too little or no air is injected, withdrawing the medication may be difficult. If too much air is injected, the plunger may be forced out of the barrel causing the medication to spill.
11. Turn the vial upside down, with the needle remaining in the vial. The needle will be pointing upward.
12. Make sure that the tip of the needle is completely covered by the medication. This will make it easier to withdraw the solution (and not air).
13. Pull back on the plunger to fill the syringe with the correct dose of medication.
14. Keep the vial upside down, with the needle in the vial pointed upward. Tap the syringe, or “flick” it with your fingertips. This helps move bubbles to the top of the syringe.
15. Once the bubbles are at the top of the syringe, gently push on the plunger to force the bubbles out of the syringe and back into the vial.

Or, you may push all the medication solution back into the vial, withdraw again slowly, and repeat steps 14 and 15.

*Note: It is important to eliminate large air bubbles because they take up space needed for the medication, and they may cause pain or discomfort when injected.*

16. After removing the bubbles, check the dose of medication in the syringe to be sure you have drawn up the correct amount.

**If using a pen, skip steps 5 to 16. Do the following:**

- a. Attach needle to pen by cleaning the top with alcohol and screwing on the needle.
- b. Dial in your prime volume (usually 0.02 mL) using the manufacturer’s directions.
- c. With pen needle pointed up, push the injection button completely. You should see a drop or stream of liquid. If you do not, repeat priming steps until this occurs.
- d. Dial in prescribed dose of medication.

17. After the medication is correctly drawn up, carefully replace the needle cap to prevent contamination.

### **Rotating injection sites**

- It is extremely important to rotate sites to keep the skin healthy. Repeated injections in the same spot can cause scarring and hardening of fatty tissue that will interfere with absorption of medication. Each injection should be about 1 inch apart. Each injection site can be measured with a small dot Band-Aid, providing the patient is not sensitive to the adhesive.
- Start injections at the highest point of the area and continue down toward the point farthest away from the body (for example, upper arm down toward elbow). It is preferable to use all sites available on one body part (arm or leg) before moving on to another. However, some parents find that children are more accepting of injections if they are rotated from one body part to another (arm, leg, arm, leg). Avoid giving injections in areas that are burned, reddened, inflamed, swollen, or damaged by prior injections.

### Preparing the skin

- Since the skin is the body’s first defense against infection, it must be cleansed thoroughly before a needle is inserted.
- Cleanse the skin with a back-and-forth motion using an alcohol swab. This motion moves bacteria away from the injection site. Allow the alcohol to dry completely by air.

### Giving the injection

1. Take the cover off the needle. Be careful not to contaminate the needle. Place the cover on its side.
2. Hold the syringe in one hand like pencil or a dart.
3. Grasp the skin between the thumb and index finger with your other hand and pinch up.
4. Quickly thrust the needle all the way into the skin. Do not “push” the needle into the skin slowly or thrust the needle into the skin with great force. Do not press down on the top of the plunger while piercing the skin.
5. Insert the needle at a 90-degree (right) angle. This angle is important to ensure that the medications will be injected into the fatty tissue. However, for small children, and persons with little subcutaneous fat on thin skin, you may be taught to use a 45-degree angle.

**If using a pen**, insert the pen needle at a 90-degree angle.

6. After the needle is completely inserted into the skin, release the skin that you are grasping. Press down on the plunger to release medication into the subcutaneous layer in a slow, steady pace.

**If using a pen**, press the injection button completely (or until it clicks). Count 10 seconds before removing the needle from the skin.

7. As the needle is pulled out of the skin, gently press a 2 x 2 gauze onto the needle insertion site. Pressure over the site while removing the needle prevents skin from pulling back, which may be uncomfortable. The gauze also helps seal the punctured tissue and prevents leakage,
8. If instructed to do so, press or rub the site for a few seconds.
9. It is not serious if you notice blood at the site after the needle is removed. You may have nicked a surface blood vessel when you injected, and blood is following the needle track out to the surface. Simply press the site with a 2 x 2 gauze pad. Also, a small amount of clear fluid may appear at the site. This may be medication that is following the needle track to the surface. Again, apply pressure using a 2 x 2 gauze pad.

**If using a pen:** Untwist needle on the pen and safely dispose the needle. Replace pen cap and store as instructed.

### Safe needle disposal

Please refer to the Clinical Center pamphlet “Handling Sharp Objects Safely at Home.”

- Place the syringe or needle in a hard plastic or metal container with a tightly secured lid.
- Do not re-cap needles after use. Keep the container out of the reach of children or pets.
- When the container is three-quarters full, take it to a health care facility (hospital or doctor’s office) for proper disposal. If you live within driving distance of NIH, you can bring your container to NIH for proper disposal.

Medication
Dose
Schedule
Primary Nurse
Phone
Physician
Phone

This information is prepared specifically for persons taking part in clinical research at the National Institutes of Health Clinical Center and may not apply to patients elsewhere. If you have questions about the information presented here, talk to a member of your health care team. Products/resources named serve as examples and do not imply endorsement by NIH. The fact that a certain product/resource is not named does not imply that such product/resource is unsatisfactory.

National Institutes of Health Clinical Center  
Bethesda, MD 20892  
Questions about the NIH Clinical Center?  
<http://www.cc.nih.gov/comments.shtml>  
09/2015

