Clinical Study Protocol

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

Study Number TV48125-CNS-30058

NCT03107052

Protocol with Amendment 04 Approval Date: 28 August 2018

Clinical Study Protocol with Amendment 04

Study Number TV48125-CNS-30058

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

Safety and Efficacy Study (Phase 3)

IND number: 129606

EudraCT number: 2016-003172-43

EMA Decision number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol with Amendment 04 Approval Date: 28 August 2018

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).

AMENDMENT HISTORY

The protocol for Study TV48125-CNS-30058 (original protocol dated 08 August 2016) has been amended and reissued as follows:

Amendment 04	ROW-28 August 2018 Sweden 28 August 2018
Amendment 03	ROW-26 April 2018 Sweden 07 June 2018
Amendment 02	ROW-03 May 2017 Sweden-19 October 2017 No patients randomized/enrolled to date
Amendment 01	30 November 2016 No patients randomized/enrolled to date
Protocol approval	08 August 2016
Letter of Clarification-USM	ROW-04 April 2018 US-06 April 2018
Letter of Clarification 08	14 March 2018
Letter of Clarification 07 (Sweden Only)	18 October 2017
Letter of Clarification 06	27 August 2017
Letter of Clarification 05	10 May 2017
Letter of Clarification 04	13 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 04

Original Protocol Dated 08 August 2016

IND number: 129606; EudraCT number: 2016-003172-43

EMA Decision number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

Principal Investigator: _____

Title: _____

Address of Investigational Center: _____

_____

Tel: _____

I have read the protocol with Amendment 04 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 agreement with 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 were furnished to me by the sponsor to all physicians and other study personnel reporting 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, investigational medicinal products (IMP) shipment and return forms, and all other information collected during the study, in accordance with national and local Good Clinical Practice (GCP) regulations as well as all other national and international laws and regulations.

Principal Investigator	**Signature**	**Date**

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	**Signature**	**Date**
[redacted]	[redacted]	28 AUG 2018

COORDINATING INVESTIGATOR AGREEMENT

Clinical Study Protocol with Amendment 04

Original Protocol Dated 08 August 2016

IND number: 129606; EudraCT number: 2016-003172-43

EMA Decision number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

I have read the protocol with Amendment 04 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 were 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: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator	Signature	Date
[redacted]		

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 04

Study TV48125-CNS-30058

Title of Study: A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache

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

Investigational New Drug (IND) Number: 129606

EudraCT Number: 2016-003172-43

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: Safety and Efficacy Study (Phase 3)

Indication: Cluster headache (CH)

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: Approximately 42 months**,** Q1/2017 (first patient in) to Q2/2020 (last patient last visit)

Number of Patients Planned (total): Prior to 15 June 2018, up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.

Prior to 15 June 2018, patients rolled over from the episodic TV48125-CNS-30056 and chronic TV48125-CNS-30057 cluster headache studies into the Long Term Safety study (TV48125-CNS-30058).

As of 15 June 2018, the chronic cluster headache (CCH) Study TV48125-CNS-30057 was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. Thus, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the anti-drug antibody (ADA) and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

As of 15 June 2018, only patients from the episodic cluster headache (ECH) Study TV48125-CNS-30056 will enroll in this study for active treatment.

Study Population: The study population will be composed of male and female patients, 18 to 70 years of age, inclusive, with a history of CH (chronic and episodic forms), as defined by International Classification of Headache Disorders, third revision beta criteria (Headache Classification Committee of the International Headache Society 2013), who participated in the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) prior to 15 June 2018. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment.

Primary and Secondary Objectives and Endpoints:

As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.

Objectives	Endpoints
The **primary objective** of this study is to evaluate the long-term safety of fremanezumab in adult patients with CH.	Safety endpoints are as follows: • occurrence of adverse events throughout the study • changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results • changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in vital signs (pulse, systolic and diastolic blood pressure, and oral temperature) measurements 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. • abnormal standard 12-lead electrocardiogram (ECG) findings • clinically significant changes in physical examination, including body weight • occurrence of injection site reactions (ie, erythema, induration, and ecchymosis) and injection site pain • occurrence of anaphylaxis and hypersensitivity reactions • use of concomitant medications during the study • suicidal ideation and behavior as measured by the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS)
There are no **secondary objectives** and secondary endpoints in this study.	

Immunogenicity Assessment Objectives and Endpoints:

The immunogenicity objective is:

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

The immunogenicity endpoints are:

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

Exploratory Objectives and Endpoints:

Exploratory objectives are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Wearable sensor substudy exploratory objectives are the following:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Wearable sensor substudy exploratory endpoints are the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

General Design:

This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).

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 TV 48125-CNS-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.

Prior to 15 June 2018, up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study as summarized in Table 1. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

Table 1: Summary of Treatments During Study TV48125-CNS-30058

Study number	Treatment group in pivotal study	Treatment in the long-term safety extension study[a, b]
Study TV48125-CNS-30056 (ECH)	Fremanezumab 900-mg iv loading dose group[c]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Fremanezumab 675-mg sc quarterly group[d]	Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36
	Placebo group[e]	Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36
Study TV48125-CNS-30057 Prior to 15 June 2018 termination of CCH Study TV48125-CNS-30057. No additional CCH patients will be enrolled after 15 June 2018 for active treatment.	Fremanezumab 900-mg iv loading dose group[c]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Fremanezumab 675-mg sc loading dose group[f]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Placebo group[e]	Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36

[a] In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30056, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of test IMP (1.5 mL-injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visits 1, 4, 7, and 10, and a single sc injection of test IMP or placebo IMP at visits 2, 3, 5, 6, 8, and 9.

[b] In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30057, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of either test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visit 1, and patients will receive a single sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) at all other visits.

[c] Fremanezumab at 900 mg iv at visit 2 (week 0) of the pivotal study and fremanezumab at 225 mg sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[d] Fremanezumab at 675 mg sc at visit 2 (week 0) of the pivotal study and placebo sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[e] Placebo iv and sc at visit 2 (week 0) of the pivotal study and placebo sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[f] Fremanezumab at 675 mg sc at visit 2 (week 0) of the pivotal study and fremanezumab at 225 mg sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

CCH=chronic cluster headache; ECH=episodic cluster headache; IMP=investigational medicinal product; iv=intravenous; sc=subcutaneous.

Patients with a diagnosis of ECH who experience CH remission, defined as no CH attacks for 12 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in

the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart treatment at their previous dose regimen through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment at 675 mg subcutaneous (sc) quarterly through week 36.

Patients with a diagnosis of CCH who experience CH remission, defined as no CH attacks for 24 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart fremanezumab treatment at 225 mg sc monthly through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment with a 675-mg sc loading dose followed by 225-mg sc monthly through week 36. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

All patients will return to the study center approximately every 4 weeks after administration of the first dose of the IMP (visit 1 [week 0]) through the end-of-treatment (EOT) visit (visit 11 [week 40]), which will occur approximately 4 weeks after administration of the last dose of the IMP (week 36). Patients will return for a follow-up visit (visit 12) to evaluate ADAs, biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of the IMP. Patients who withdraw from the study before completing the 40-week treatment period will have EOT visit procedures and assessments performed on the last day the patients received the IMP or as soon as possible thereafter, and they will be asked to return for a follow-up visit approximately 7.5 months after their last dose of the IMP.

Patients who enter the long-term safety follow-up study for safety follow-up only will not follow the same visit schedule as that for patients receiving treatment. The procedures and assessments for the patients participating in the safety follow-up are described in Table 5.

CH attack information will be captured daily throughout the treatment period (ie, visit 1 [week 0] through visit 11 [week 40]) using an electronic diary device. Assessments of change in quality of life, satisfaction with treatment, 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 Patient Perceived Satisfactory Improvement 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 pre-specified time points.

The long-term 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 assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS.

Wearable Sensor Substudy: Patients rolling over from the Phase 3 pivotal efficacy studies who also enrolled in the wearable sensor substudy will be allowed to continue in this substudy during this long-term safety extension study provided they consent to continuing their participation. These patients will return to the investigational center for up to 2 additional visits after any dose of the IMP for blood sampling for pharmacokinetics analysis, triplicate 12-lead ECGs, and inquiries about adverse events and concomitant medications. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

Brief Summary of Study Design for the Trial Registry(s):

This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. Patients who complete the pivotal studies and enroll into the current study (at visit 1 [week 0]) will visit the investigational center approximately every 4 weeks for 36 weeks for IMP administration (fremanezumab at 675 mg sc quarterly, 225 mg sc monthly, or a loading dose of 675 mg sc followed by 225 mg sc monthly), safety assessments, and blood and urine collections for pharmacokinetics, immunogenicity (ADAs), and biomarker analyses. An EOT visit will occur approximately 4 weeks after administration of the last dose of IMP. Patients will return to the investigational center for a follow-up visit to evaluate ADAs, biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of IMP.

The long-term 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 assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. 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, satisfaction with treatment, and health status. In addition, blood will be collected for pharmacokinetics, immunogenicity, and biomarkers, (blood for pharmacogenomics is collected during the pivotal studies), and urine will be collected for biomarker analysis.

Method of Randomization and Blinding:

This is a double-blind study; blinding will be retained from the pivotal studies and throughout this long-term safety extension study. Patients will be assigned to treatments as described in Table 1 based on their randomization in the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057). Refer to the protocols for the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) for details regarding randomization of patients in this study. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

Packaging vendor(s) will package test IMP and placebo IMP into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance. Adequate kit supply for upcoming study visits will be managed by interactive response technology (IRT) and kept (refrigerated at 2°C to 8°C) at the investigational centers.

At visits 1 through 10, the IRT will be queried, and investigational center personnel will retrieve and administer each prefilled syringe contained in the appropriately numbered kit(s). Kit numbers will be entered into the case report form.

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.

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

IMPs are defined as the test IMP and placebo IMP (Table 2).

Table 2: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	Fremanezumab (TEV-48125 [formerly LBR-101, PF-04427429, or RN307])	n/a
Formulation	Solution for injection	Solution for injection
Unit dose strength(s) dosage level(s)	225 mg/1.5 mL 675 mg sc quarterly, 225 mg sc monthly, or 675 mg sc loading dose followed by 225 mg monthly	n/a
Route of administration	Fremanezumab will be administered as sc injections (1.5 mL per injection) by qualified study personnel at the study center.	Placebo will be administered as sc injections (1.5 mL per injection) by qualified study personnel at the study center.
Packaging	Fremanezumab will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) at the investigational centers. Prefilled syringes (1.5 mL) 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) at the investigational centers. Prefilled syringes (1.5 mL) will contain the same vehicle and excipients as those for active infusion and injection.
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]

IMP=investigational medicinal product; INN=International Nonproprietary Name; n/a=not applicable; sc=subcutaneous.

Patients who received fremanezumab during the pivotal studies at 225 mg sc monthly after a loading dose of 900-mg intravenously or 675 mg sc or fremanezumab at 675 mg sc quarterly during the pivotal studies will continue receiving the same dose (ie, 225 mg sc monthly or 675 mg sc quarterly depending upon their diagnosis and randomization in the pivotal studies) during this long-term safety extension study. These dose regimens are expected to maintain steady state at a blood concentration level that will provide clinical efficacy. The doses and

dosing regimens also account for the natural history of the 2 forms of CH; patients with ECH are likely to remit after initial treatment whereas CCH patients are continuously inflicted by pain.

Patients who received placebo during the pivotal studies will be assigned to receive either fremanezumab 675 mg sc quarterly (patients with ECH from Study TV48125-CNS-30056) or a loading dose 675 mg sc followed by monthly fremanezumab at 225 mg sc monthly (patients with CCH from Study TV48125-CNS-30057). This will provide these patients with the opportunity to receive potential benefit from therapeutic doses including the loading dose of 675 mg sc. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete further safety follow-up visits and will be discharged from the study.

When the cluster cycle is almost over in ECH, the number of headache attacks per day start to decrease with associated mild to moderate intensity. Patients often look for preventive options in the very early part of the headache cycle in an attempt to reduce its duration. Equally, when complete remission is achieved patients with ECH consider stopping their medication and thus withdraw from treatment when the cluster period is over (May 2005). Accordingly, continuous long-term treatment in ECH might not be needed as these patients may have long remission periods between the cluster episodes. Patients with CCH may face a different situation, where the remission period is very short (less than a month). These patients might be more inclined to continue with long-term preventive treatment. Thus, the current study will evaluate the concept of intermittent treatment in both ECH and CCH; IMP administration may be discontinued in patients with CH remission (defined in ECH as patients with at least 12 successive weeks of no CH attacks at any time after starting IMP and in CCH as patients with at least 24 successive weeks of no CH attacks at any time after starting IMP).

Differentiating between remission periods lasting 12 weeks or less and remission period lasting more than 12 weeks after treatment has been stopped, dictates the need for the administration of a loading dose of fremanezumab at 675 mg sc when remission lasted for more than 12 weeks (as most of the drug is eliminated after 12 weeks). Thereafter, the doses and dosing regimens are identical to those in the pivotal studies for each CH form (ie, 225 mg sc monthly for CCH and 675 mg sc quarterly for ECH). If treatment is stopped and headache attacks restart within 12 weeks of stopping the treatment, patients will proceed with their previous dose, which is expected to re-establish efficacy and which maintains the differentiation between the 2 CH forms. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

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: Participation of patients who enroll in this study for the purpose of evaluating the long-term safety and efficacy of

fremanezumab will last for approximately 68 weeks (not including participation in the Phase 3 pivotal efficacy studies).

Study Duration: Approximately 42 months from Q1/2017 to Q2/2020

End of Study: End of study is defined as the date the last patient attends the follow-up visit.

Plans for Treatment or Care after the Patient Has Ended Participation in the Study: Not applicable

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

a. The patient is a male or female and 18 to 70 years of age, inclusive, at the start of the pivotal study.

b. The patient signs and dates the informed consent document.

c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study. Prior to 15 June 2018, patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

   – In addition, patients who do not complete the pivotal efficacy studies, and patients who complete the pivotal efficacy studies but will not continue treatment during this long-term safety study, will be offered to enroll in this 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 the IMP.

d. Women may be included only if they have a negative beta-human chorionic gonadotropin test at visit 1; are sterile or postmenopausal; and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.

e. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP.

   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 administration of IMP.

   Definitions of women of non-childbearing potential, sterile and postmenopausal women; male contraception; and highly effective and acceptable birth control methods, including examples, are given in Appendix E.

f. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH (ie, verapamil, topiramate, valproate, lithium, or methysergide) for the duration of this study. Patients must begin tapering these preventive medications as soon as they begin this study. The period of time needed to taper off these medications will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study (Appendix H) (not applicable for patients participating in safety follow-up only).

g. 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 (not applicable for patients participating in safety follow-up only).

h. 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 a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.

b. Any finding in the 12-lead ECG performed as part of the EOT visit (visit 5) procedures for the pivotal studies considered clinically significant in the judgment of the investigator

c. 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)

d. Hepatic enzymes (alanine aminotransferase and aspartate aminotransferase) >1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law

e. Serum creatinine >1.5 × the ULN or evidence of clinically significant renal disease in the judgment of the investigator

Patients rolling over only for safety follow-up and ADA, who are not receiving study medication, are not required to fulfil all inclusion exclusion criteria.

Statistical Considerations:

Sample Size Rationale: Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.

The sample size for each of the pivotal studies TV48125-CNS-30056 for ECH and TV48125-CNS-30057 for CCH is approximately 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately 360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.

Prior to 15 June 2018, patients from ECH TV48125-CNS-30056 and CCH TV48125-CNS-30057 studies were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

Analysis of Primary Endpoint: The primary endpoints for this study are related to safety. Refer to the safety analysis section below for details.

Analysis of Secondary Endpoints: Not applicable

Primary Efficacy Analysis: Not applicable

Sensitivity Analysis: Not applicable

Secondary Efficacy Analysis: Not applicable

Multiple Comparisons and Multiplicity: Not applicable

Exploratory Efficacy Analysis:

All efficacy variables will be summarized descriptively overall, by indication (ECH or CCH), and by treatment group. For continuous variables, descriptive statistics (number of patients [n], mean, standard deviation [SD], and standard error of mean, median, minimum, and maximum) will be provided for actual values and changes from baseline to each visit. For categorical variables, frequency and percentage will be provided.

Baseline is defined as the baseline in the pivotal efficacy studies.

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. Summaries will be presented by treatment group and for all patients. 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 measurements data will be summarized descriptively. All values will be compared with pre-specified 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.

Suicidal ideation and behavior will be measured using the eC-SSRS. Data for patients with positive findings will be listed.

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: Pharmacokinetic plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by diagnosis (ECH or CCH) and by treatment.

In addition, the most appropriate population pharmacokinetic 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 parameters may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy/safety 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 parameters 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 pharmacokinetic profile, IMP efficacy, and clinical safety will be evaluated. This ADA-impact analysis will be reported separately.

Exploratory Biomarker Analysis: Exploratory biomarker measurements will be made using appropriately validated assays. Results, if generated, will typically be expressed as % change from baseline and reported in a separate addendum report.

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 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.

Planned Interim Analysis: Not applicable

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	antidrug antibody
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
β-HCG	beta-human chorionic gonadotropin
CBC	complete blood cell
CCH	chronic cluster headache
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGRP	calcitonin gene-related peptide
CH	cluster headache
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CL/F	apparent total plasma clearance
C_{max}	maximum observed concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	Electrocardiogram
ECH	episodic cluster headache
EFD	embryo/fetal developmental toxicity
EOT	end-of-treatment
EQ-5D	EuroQol-5 Dimension
FAS	full analysis set
FSH	follicle-stimulating hormone
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 Council for Harmonisation
ICHD	International Classification of Headache Disorders-third edition beta

Abbreviation	Term
IEC	Independent Ethics Committee
Ig	Immunoglobulin
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
n	number of patients
PEF	peak expiratory flow
PGIC	Patient Global Impression of Change
PPSI	Patient-Perceived Satisfactory Improvement
RSI	reference safety information
RTSM	Randomization and Trial Supply Management
sc	subcutaneous(ly)
SD	standard deviation
SF-12	12-Item Short-Form Health Survey
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum observed concentration
ULN	upper limit of the normal range
VIP	vasoactive intestinal peptide
V_{ss}	volume of distribution at steady state
V_z/F	apparent total volume of distribution during the terminal phase
WOCBP	women of childbearing potential
WPAI	Work Productivity and Activity Impairment

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

1.1.1. 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.

1.1.2. 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 (α- and β-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 [redacted]. 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.

1.1.3. Study Purpose

The purpose of the current study is to evaluate the long-term safety and efficacy of fremanezumab administered subcutaneously (sc) to adult patients with CH.

Prior to 15 June 2018, patients rolled over from the episodic TV48125-CNS-30056 and chronic TV48125-CNS-30057 cluster headache studies into the Long Term Safety study (TV48125-CNS-30058).

As of 15 June 2018, CCH Study TV48125-CNS-30057 was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. The planned interim analysis was for futility evaluation based on 50% of patients (ie, the first 150 patients who had completed the study or withdrawn from the study early). An independent unblinded statistician from a third party performed the analysis. The futility evaluation was assessed using conditional power. The sponsor was notified that the conditional power was less than 25% for both comparisons (fremanezumab 900 mg iv loading dose group versus placebo or fremanezumab 675 mg sc loading dose group versus placebo). Thus, all CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment.

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.

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}.

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, low volume of distribution at steady state (V_{ss}), and a long terminal elimination half-life ($t_{½}$). 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

The clinical pharmacology development (Phase 1) program for fremanezumab in migraine includes 8 completed studies. A total of 318 healthy subjects were enrolled, of which 256 subjects received at least 1 dose of fremanezumab. [redacted]. A description of the objectives of these 6 Phase 1 studies is as follows:

- Studies B0141001 and B0141002 were iv single-dose escalation PK and PD studies in healthy men.
- Study B0141006 was a 2-cohort, placebo-controlled crossover study to examine the acute effects of iv administration of fremanezumab on capsaicin flare response in healthy men.
- Study B0141007 was a parallel-group, repeat-dose PK and PD study of iv administration of fremanezumab in healthy men and women.
- Study LBR-101-008 was a single-dose study examining the safety, tolerability, PK, and PD of doses up to 2000 mg of fremanezumab administered iv to healthy women.
- Study LBR-101-011 was a randomized, placebo-controlled, double-blind, parallel-group study examining the safety, tolerability, absolute bioavailability (BA), and PK of 2 different single doses of fremanezumab administered iv or sc to healthy men and women.

Two additional Phase 1 studies, Studies TV48125-PK-10078 and TV48125-BE-10114, were conducted using the current validated bioanalytical method. A description of the objectives of these 2 Phase 1 Studies is as follows:

- Study TV48125-PK-10078 was a randomized, double-blind, placebo-controlled study to assess the PK, safety, and tolerability of single-dose sc administration of fremanezumab (single ascending doses and single doses up to 900 mg) in Japanese and Caucasian healthy subjects.

- Study TV48125-BE-10114 was an open-label, single-dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women.

Additional ongoing bioequivalence study (TV48125-BE-10145) is another open-label, single-dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women.

The pharmacokinetics (non-compartmental analysis; Study TV48125-PK-10078) of fremanezumab demonstrated an increase in C_{max} and AUC values slightly greater than the dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values was generally 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-mg 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 $t_{½}$ ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects.

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 swelling, injection site pain, injection site pruritus, injection site dermatitis, injection site rash, injection site edema, 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, injection site rash, injection site induration, and injection site pruritus. 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 fremanezumab 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.

The benefit and risk assessment for fremanezumab has been re-assessed for patients with CCH. As of 15 June 2018, the CCH study (Study TV48125-CNS-30057) was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. Thus, all CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study. Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.

The primary and secondary study objectives and endpoints are:

Objectives	**Endpoints**
The **primary objective** of this study is to evaluate the long-term safety of fremanezumab in adult patients with cluster headache (CH).	Safety endpoints are as follows: • occurrence of adverse events throughout the study • changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in clinical laboratory (serum chemistry, hematology, coagulation, and urinalysis) test results • changes from baseline (day 0 of the Phase 3 pivotal efficacy studies) in vital signs (pulse, systolic and diastolic blood pressure, and oral temperature) measurements • 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. • abnormal standard 12-lead electrocardiogram (ECG) findings • clinically significant changes in physical examination, including body weight • occurrence of injection site reactions (ie, erythema, induration, and ecchymosis) and/or injection site pain • occurrence of anaphylaxis and hypersensitivity reactions • use of concomitant medications during the study • suicidal ideation and behavior as measured by the electronic Columbia Suicide Severity Rating Scale (eC-SSRS)
There are no **secondary objectives** and secondary endpoints in this study.	

Objectives	Endpoints
The **immunogenicity objective** is to evaluate the immunogenicity of fremanezumab and the impact of antidrug antibodies (ADAs) on clinical outcomes in patients exposed to fremanezumab	The immunogenicity endpoints are ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities)

2.1.1. Justification of Primary Endpoint

The primary endpoints are standard safety endpoints for clinical studies to evaluate the long-term safety of a drug. Endpoints related to injection site reactions/injection site pain and anaphylaxis/hypersensitivity reactions are included based on identified risks of fremanezumab (see Section 1.3.1).

2.2. Exploratory Objectives and Endpoints

2.2.1. Exploratory Objectives and Endpoints

Exploratory objective are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]

2.2.2. Wearable Sensor Substudy Exploratory Objectives and Endpoints

Wearable sensor substudy exploratory objectives are the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Wearable sensor substudy exploratory endpoints are the following:

- [redacted]
- [redacted]

[redacted]

3. STUDY DESIGN

3.1. General Design and Study Schematic Diagram

This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).

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 this study protocol) 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-CNS-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.

Prior to 15 June 2018, up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized in Table 3. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

Table 3: Summary of Treatments During Study TV48125-CNS-30058

Study number	Treatment group in pivotal study	Treatment in the long-term safety extension study[a, b]
Study TV48125-CNS-30056 (ECH)	Fremanezumab 900-mg iv loading dose group[c]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Fremanezumab 675-mg sc quarterly group[d]	Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36
	Placebo group[e]	Fremanezumab at 675 mg sc quarterly (approximately every 12 weeks) through week 36
Study TV48125-CNS-30057 (CCH) Prior to 15 June 2018 termination of CCH Study TV48125-CNS-30057. No additional CCH patients will be enrolled after 15 June 2018 for active treatment.	Fremanezumab 900-mg iv loading dose group[c]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Fremanezumab 675-mg sc loading dose group[f]	Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36
	Placebo group[e]	Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36

[a] In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30056, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visits 1, 4, 7, and 10, and a single sc injection of test IMP or placebo IMP at visits 2, 3, 5, 6, 8, and 9.

[b] In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30057, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of either test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visit 1, and patients will receive a single sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) at all other visits.

[c] Fremanezumab at 900 mg iv at visit 2 (week 0) of the pivotal study and fremanezumab at 225 mg sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[d] Fremanezumab at 675 mg sc at visit 2 (week 0) of the pivotal study and placebo sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[e] Placebo iv and sc at visit 2 (week 0) of the pivotal study and placebo sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

[f] Fremanezumab at 675 mg sc at visit 2 (week 0) of the pivotal study and fremanezumab at 225 mg sc at visits 3 and 4 (weeks 4 and 8, respectively) of the pivotal study.

CCH=chronic cluster headache; ECH=episodic cluster headache; IMP=investigational medicinal product; iv=intravenous; sc=subcutaneous.

Patients with a diagnosis of ECH who experience CH remission, defined as no CH attacks for 12 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the

subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart treatment at their previous dose regimen through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment at 675 mg sc quarterly through week 36.

Patients with a diagnosis of CCH who experience CH remission, defined as no CH attacks for 24 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart fremanezumab treatment at 225 mg sc monthly through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment with a 675-mg sc loading dose followed by 225-mg sc monthly through week 36. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

All patients will return to the investigational center approximately every 4 weeks after administration of the first dose of the IMP (visit 1 [week 0]) through the end-of-treatment (EOT) visit (visit 11 [week 40]), which will occur approximately 4 weeks after administration of the last dose of the IMP (week 36). Patients will return for a follow-up visit (visit 12) to evaluate ADAs, biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of the IMP. Patients who withdraw from the study before completing the 40-week treatment period will have EOT visit procedures and assessments performed on the last day the patients received the IMP or as soon as possible thereafter, and they will be asked to return for a follow-up visit approximately 7.5 weeks after their last dose of IMP.

Patients who enter the long-term safety follow-up study for safety follow-up only will not follow the same visit schedule as that for patients receiving treatment. The procedures and assessments for the patients participating in the safety follow-up are described in Table 5.

CH attack information will be captured daily throughout the treatment period (ie, visit 1 [week 0] through visit 11 [week 40]) 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 Patient-Perceived Satisfactory Improvement [PPSI] and the Patient Global Impression of Change [PGIC] scale); safety evaluations; blood collection for pharmacokinetic, immunogenicity, and biomarker analyses; and urine sampling for biomarker analysis will be performed at pre-specified time points (Table 4).

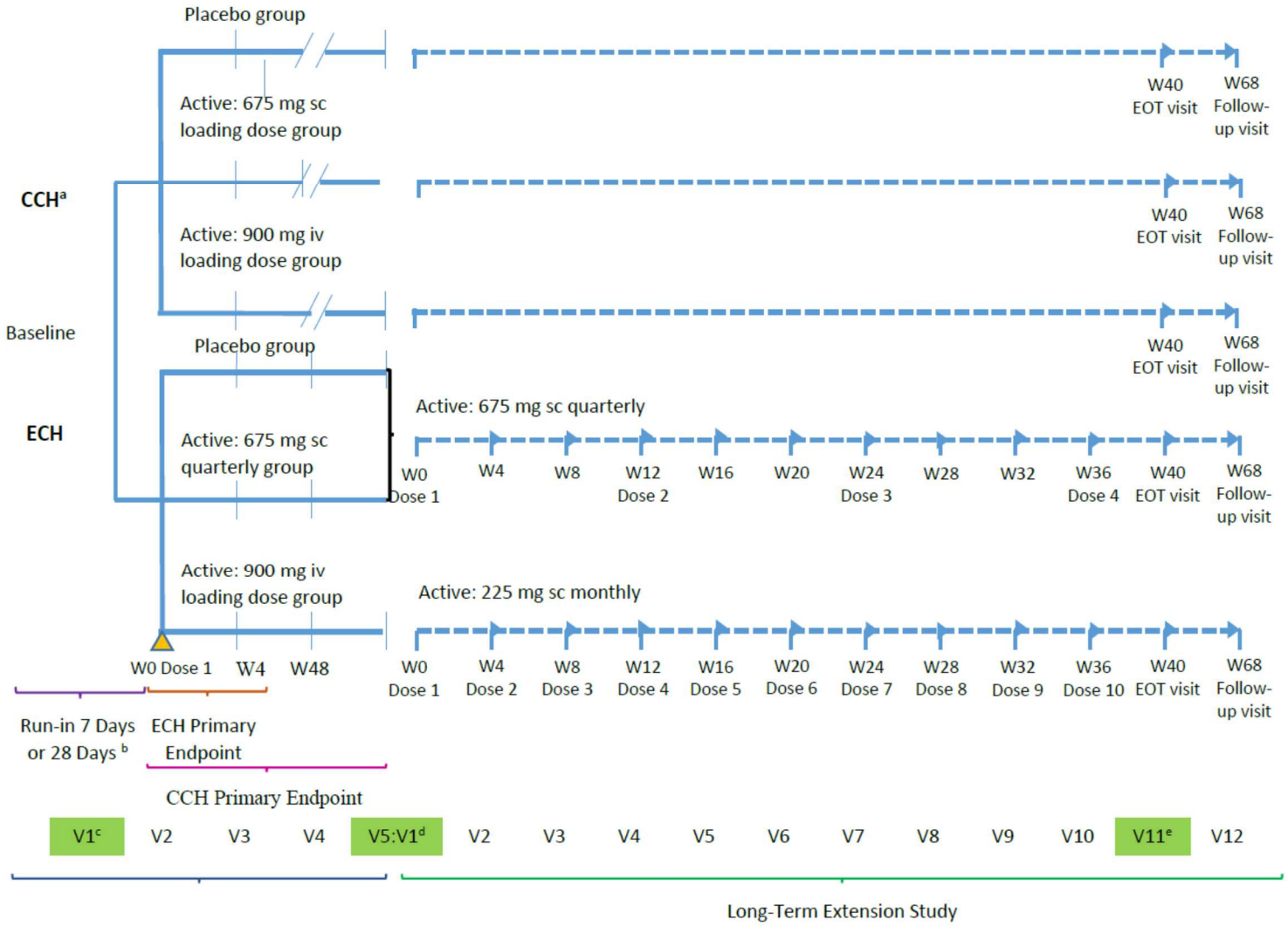
The long-term safety of fremanezumab in patients with CH will be evaluated through adverse event and concomitant medication inquiries, ECGs, vital signs measurements, clinical laboratory tests, physical examinations, injection site assessments, assessments for anaphylaxis and hypersensitivity, and administration of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS).

The end of study is defined as the date the last patient attends the follow-up visit.

The study duration will be for approximately 42 months, from Q1/2017 to Q2/2020.

The study schematic diagram for patients enrolling in this study for the purpose of evaluating the long-term safety and efficacy of fremanezumab is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



[a] As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

[b] The run-in period for patients with ECH lasted at least 7 days (+3 days), and the run-in period for patients with CCH lasted at least 28 days (+3 days).

[c] Screening will occur at visit 1 of the Phase 3 pivotal efficacy studies. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

[d] Visit 1 of this study corresponds to the EOT visit (visit 5) of the pivotal efficacy studies. The EOT visit procedures/assessments for the pivotal efficacy study must be completed before beginning visit 1 procedures/assessments. EOT visit procedures/assessments will not be repeated at visit 1 of this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057.

[e] Visit 11 corresponds to Visit 1 for the ADA and Safety follow-up portion of this study.

ADA=anti-drug antibody; CCH=chronic cluster headache; ECH=episodic cluster headache; EOT=end-of-treatment; iv=intravenous; pts=patients; sc= subcutaneous; V=visit; W=week.

Note: Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.

Wearable Sensor Substudy: This substudy is being conducted 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). Patients rolling over from the Phase 3 pivotal efficacy studies who also enrolled in the wearable sensor substudy will be allowed to continue in this substudy during this long-term safety extension study. [redacted] After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

3.2. Planned Number of Patients and Countries

Prior to 15 June 2018, up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment.

The study is planned to be conducted in approximately 12 countries in approximately 80 investigational centers. The study is expected to start in Q1/2017 (first patient in) and last until approximately Q2/2020 (last patient last visit).

3.3. Justification for Study Design and Selection of Population

It is very important to recognize the significant difficulty of asking patients with CH to continue in a double-blind, placebo-controlled study beyond 3 months. Hence, in the current study, all patients will receive fremanezumab so that all patients have the opportunity to receive potential benefit from therapeutic doses including the loading dose of 675 mg sc. The dosing regimens planned for this study are consistent with dosing regimens in the pivotal studies. Refer to Section 5.3 for additional details regarding the rationale for the doses and dose regimens.

This study is double-blind to ensure impartiality in evaluating the long-term safety and efficacy of different dose regimens of fremanezumab and to avoid unblinding the pivotal studies before they are completed. The blind will be maintained according to standard blinding procedures (see Section 5.9.2) and through the use of dummy injections to ensure that number of injections is the same at each visit for patients with ECH and patients with CCH (see Section 5.1.1.1). After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

The study population will be composed of male and female patients, aged 18 to 70 years, inclusive, with a history of CCH or ECH (as defined by International Classification of Headache Disorders-third edition beta [ICHD-3 beta] criteria [Headache Classification Committee of the IHS 2013]) for at least 12 months prior to screening. Concomitant medications that are commonly prescribed for the preventive treatment of CH (listed in Appendix H) are prohibited throughout this study so that effects of the test IMP can be distinguished from effects of these concomitant preventive medications. Thus, patients who were taking concomitant preventive

medications during the pivotal studies will be required to taper off these medications during the first month of treatment in this study.

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

There are no formal rules for early termination of this 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 that:

- new toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment
- discontinuation of the development of the IMP

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 Appendix C, 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, or indirect], or international normalized ratio [INR]) may meet criteria for discontinuation from the IMP as summarized in Appendix J.

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points for patients enrolling in this study from the pivotal efficacy studies for treatment are presented in Table 4. Assessments and procedures for patients rolling over from the pivotal efficacy studies for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) only is presented in Table 5. 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 4: Study Procedures and Assessments for Treated Patients

	Double-blind treatment period[a]											**Follow-up period**
Visit number	**V1**[b]	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Week 0 (day 0)**	**Week 4 (±3 days)**	**Week 8 (±3 days)**	**Week 12 (±3 days)**	**Week 16 (±3 days)**	**Week 20 (±3 days)**	**Week 24 (±3 days)**	**Week 28 (±3 days)**	**Week 32 (±3 days)**	**Week 36 (±3 days)**	**EOT/early withdrawal week 40 (±3 days)**	**Follow-up week 68 (±1 week)**[c]
Informed consent	X[d,e]											
Inclusion and exclusion criteria	X											
Taper current preventive medication[f]	X											
Full physical examination, including weight		X		X	X		X	X		X	X	X
Triplicate 12-lead ECG[g,h]				X			X			X	X	
Vital signs measurement[g]		X	X	X	X	X	X	X	X	X	X	X
Adverse events[i]	X[j]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry		X	X	X	X	X	X	X	X	X	X[k]	X
Clinical laboratory tests[l,m]				X			X			X	X	
Serum β-HCG test[n]											X	
Urine β-HCG test[n]	X	X	X	X	X	X	X	X	X	X		
eC-SSRS[o,p]		X	X	X	X	X	X	X	X	X	X	X
Enter cluster headache attack information in the electronic diary device[q]	X										X	
Review electronic diary data		X	X	X	X	X	X	X	X	X	X	

Table 4: Study Procedures and Assessments for Treated Patients (Continued)

	Double-blind treatment period[a]											Follow-up period
Visit number	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Week 0 (day 0)**	**Week 4 (±3 days)**	**Week 8 (±3 days)**	**Week 12 (±3 days)**	**Week 16 (±3 days)**	**Week 20 (±3 days)**	**Week 24 (±3 days)**	**Week 28 (±3 days)**	**Week 32 (±3 days)**	**Week 36 (±3 days)**	**EOT/early withdrawal week 40 (±3 days)**	**Follow-up week 68 (±1 week)[c]**
Return electronic diary device											X	
Blood sample for pharmacokinetics analysis[r]		X	X	X	X	X	X	X	X	X	X	
Blood sample for serum ADA analysis[s]				X			X			X	X	X
Blood collection for serum, plasma, and RNA biomarker analysis[t]				X			X			X	X	X
Urine collection for biomarker analysis				X			X			X	X	X
HADS[p]		X					X			X	X	
EQ-5D questionnaire[p]		X					X			X	X	
SF-12[p]		X					X			X	X	
WPAI questionnaire[p]		X		X			X			X	X	
Impact on Partners and Family questionnaire[p,u]		X		X			X			X	X	
PPSI[v]		X	X	X			X			X	X	
PGIC scale[v]		X	X	X			X			X	X	
Wearable sensor substudy data capture[w]	X										X	

Table 4: Study Procedures and Assessments for Treated Patients (Continued)

	Double-blind treatment period[a]											Follow-up period
Visit number	**V1[b]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Procedures and assessments (completed before dosing, when applicable, unless otherwise noted)	**Week 0 (day 0)**	**Week 4 (±3 days)**	**Week 8 (±3 days)**	**Week 12 (±3 days)**	**Week 16 (±3 days)**	**Week 20 (±3 days)**	**Week 24 (±3 days)**	**Week 28 (±3 days)**	**Week 32 (±3 days)**	**Week 36 (±3 days)**	**EOT/early withdrawal week 40 (±3 days)**	**Follow-up week 68 (±1 week)[c]**
Wearable sensor check and compliance check		X	X	X	X	X	X	X	X	X	X	
Return wearable sensor											X	
Study IMP administration[x]	X	X	X	X	X	X	X	X	X	X		
Injection site reaction/pain assessment[y]	X	X	X	X	X	X	X	X	X	X		
Anaphylaxis and hypersensitivity reaction assessment[z]	X	X	X	X	X	X	X	X	X	X		

[a] 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.

[b] Visit 1 of the current study corresponds with the EOT visit (visit 5) of the pivotal efficacy studies. EOT visit procedures/assessments must be completed before the patient begins participation in this study, and the EOT procedures/assessments will not be repeated at visit 1 of this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057.

[c] For patients who discontinue the study early and patients who achieve CH remission (ie, meaning they stop and may restart treatment depending upon whether or not CH attacks recur), the follow-up visit will be approximately 7.5 months after the last dose of IMP.

[d] In addition to the patient, the partner or family member who will complete the Impact on Partner and Family questionnaire, if applicable, will also provide written informed consent.

[e] Patients participating in the wearable sensor substudy will be asked to provide consent to continue participating in the substudy during this long-term safety study.

[f] Current preventive medication should be tapered over 1 month from the beginning of participation in this study.

[g] Procedure/assessment will be performed before blood draws and administration of questionnaires.

[h] Electrocardiograms will be performed in triplicate, with approximately 1 to 5 minutes between recordings.

[i] Adverse events will be recorded from the time informed consent for this study is obtained through the end of study participation. Inquiries about adverse events will be made at every visit. At visits 1 through 10 inquiries about adverse events will be made before and after dosing of the IMP.

[j] The predose adverse event inquiry will be completed as part of EOT visit (visit 5) procedures for the pivotal studies.
[k] As appropriate, patients should be treated with standard of care following completion of the EOT/early withdrawal visit.
[l] Serum chemistry, hematology, coagulation, and urinalysis.
[m] Currently menstruating (yes, no, n/a) information will be collected from each female patient prior to blood and urine collection for clinical laboratory tests.
[n] WOCBP only.
[o] The eC-SSRS Since Last Visit version will be completed at every visit including unscheduled visits.
[p] Responses will be entered in the site tablet.
[q] 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) daily into the electronic diary device through visit 11 (week 40).
[r] Blood samples for pharmacokinetic analysis will be collected prior to dosing, where applicable. Patients who signed consent for the wearable sensor substudy (at the pivotal studies) only will return to the investigational center for up to 2 additional visits after any dose of the IMP for blood sampling for pharmacokinetics analysis, triplicate12-lead ECGs, and inquiries about adverse events and concomitant medications. These visits should occur during the following time periods relative to any dose of the IMP: 3 to 10 days or 15 to 20 days after IMP.
[s] Blood samples for serum ADA assessment ([redacted]) will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis.
[t] 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 RNA.
[u] Partners/family members 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.
[v] In addition to the time points presented in this table, patients will also complete this procedure/assessment at week 1. Patients will record responses at week 1 in the electronic diary, and responses at all other time points will be recorded in the site tablet.
[w] Patients rolling over from the Phase 3 pivotal efficacy studies who also enrolled in the wearable sensor substudy will be allowed to continue in the substudy during this long-term safety study provided they consent to continuing their participation at visit 1. Patients will be required to wear the digital wearable device on the wrist continuously throughout the treatment period of this study.
[x] Doses/dosing regimens will be assigned based on randomization in the pivotal studies, and dummy placebo sc injections will be administered to maintain blinding. Refer to Table 3 and Section 5.1.1.1 for additional details.
[y] Injection sites 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 IMP administration and hourly (±15 minutes) thereafter until the reaction is of moderate or less severity.
[z] Patients will be assessed for hypersensitivity reaction and anaphylaxis during and after receiving the IMP (through 1 hour postdose).

ADA=antidrug antibody; β-HCG=beta-human chorionic gonadotropin; CCH=chronic cluster headache; CH=cluster headache; CRF = case report form; ECG=electrocardiogram; ECH=episodic cluster headache; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; EOT=end-of-treatment; EQ-5D=EuroQol-5 Dimension; HADS=Hospital Anxiety and Depression Scale; IMP=investigational medicinal product; n/a=not applicable; PGIC=Patient Global Impression of Change; PPSI=Patient-Perceived Satisfactory Improvement; sc=subcutaneous; SF-12=12-Item Short-Form Health Survey; V=visit; WOCBP=women of childbearing potential; WPAI=Work Productivity and Activity Impairment.

Table 5: Study Procedures and Assessments for Patients Rolling Over from the Pivotal Efficacy Studies for Evaluation of Antidrug Antibodies and Safety (Adverse Events and Concomitant Medications) Only

Procedures and assessments	Enrollment visit	Follow-up visit
	Visit 1[a]	Visit 12
	Day 0	Approximately 7.5 months (approximately 5 half-lives of the IMP) after the last dose of the IMP during the pivotal efficacy study
Informed consent	X	
Adverse events[b]	X	X
Concomitant medication inquiry	X	X
Blood sample for ADA analysis		X

[a] Visit 1 of the current study corresponds with the EOT visit/early withdrawal visit of the pivotal efficacy studies. EOT visit procedures/assessments must be completed before the patient begins participation in this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057.

[b] Patients will return for unscheduled visits in the event of any safety concern.

ADA=antidrug antibody; EOT=end-of-treatment; IMP=investigational medicinal product.

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 (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 included in the treatment portion of the study only if they meet all of the following criteria:

a. The patient is a male or female and 18 to 70 years of age, inclusive, at the start of the pivotal study.

b. The patient signs and dates the informed consent document.

c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study. Prior to 15 June 2018, patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

   – In addition, patients who do not complete the pivotal efficacy studies, and patients who complete the pivotal efficacy studies but do not wish to continue treatment during this long-term safety study, will be offered to enroll in this 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 the IMP.

d. Women may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at visit 1, are sterile or postmenopausal, and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.

e. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP.

   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 administration of IMP.

   Definitions of women of non-childbearing potential, sterile and postmenopausal women; male contraception; and highly effective and acceptable birth control methods, including examples, are given in Appendix E.

f. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH (ie, verapamil, topiramate, valproate, lithium, or methysergide) for the duration of this study. Patients must begin tapering these preventive medications as soon as they begin this study. The period of time needed to taper off these medications will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study (Appendix H) (not applicable for patients participating in safety follow-up only).

g. 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 (not applicable for patients participating in safety follow-up only).

h. 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 be excluded from participating in the treatment portion of this study if they meet any of the following criteria:

a. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.

b. Any finding in the 12-lead ECG performed as part of the EOT visit (visit 5) procedures for the pivotal studies considered clinically significant in the judgment of the investigator.

c. 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).

d. Hepatic enzymes (ALT and AST) >1.5 × the upper limit of the normal range (ULN) after confirmation in a repeat test or suspected hepatocellular damage that fulfills criteria for Hy's law.

e. Serum creatinine >1.5 × the ULN or evidence of clinically significant renal disease in the judgment of the investigator.

Patients rolling over only for safety follow-up and ADA who are not receiving study medication are not required to fulfil all inclusion exclusion criteria.

4.3. Withdrawal Criteria and Procedures for the Patient

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

1. Patient withdraws consent or requests discontinuation from this 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 (including noncompliance with wearable sensor substudy, if applicable) in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test result.
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 enrolled 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 Table 4). Patients who withdraw from the study will not be replaced.

A patient should only be designated as lost to follow-up if the investigational center 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 enrolled but does not complete the treatment period will not be replaced.

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 placebo IMP. Details of the test and placebo IMPs are presented in Table 6.

Table 6: Investigational Medicinal Products Used in the Study

IMP name	Test IMP	Placebo IMP
Trade name and INN, if applicable, or company-assigned number	Fremanezumab (formerly LBR-101, PF-04427429, or RN 307)	n/a
Formulation	Solution for injection	Solution for injection
Unit dose strength(s) **dosage level(s)**	225 mg/1.5 mL 675 mg sc quarterly, 225 mg sc monthly, or 675 mg sc loading dose followed by 225 mg monthly	n/a
Route of administration	Fremanezumab will be administered as sc injections (1.5 mL per injection) by qualified study personnel at the investigational center.	Placebo will be administered as sc injections (1.5 mL per injection) by qualified study personnel at the investigational center.
Packaging	Fremanezumab will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) at the investigational centers. Prefilled syringes (1.5 mL) 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) at the investigational centers. Prefilled syringes (1.5 mL) will contain the same vehicle and excipients as those for active infusion and injection.
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]	Teva Branded Pharmaceutical Products R&D, Inc. [redacted]

IMP=investigational medicinal product; INN= International Nonproprietary Names; n/a=not applicable; sc=subcutaneous.

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. 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 1 through 10). 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. Additional details may be found in Table 6 and in the IB for fremanezumab.

5.1.1.1. Starting Dose and Dose Levels

Patients rolling over from Study TV48125-CNS-30056 with ECH:

- Patients who were in the fremanezumab 900-mg iv loading dose group will receive fremanezumab at 225 mg sc as a single injection at visit 1 and every 4 weeks thereafter through week 36 (visit 10). For blinding, these patients will also receive 2 placebo sc injections at visits 1, 4, 7, and 10.
- Patients who were in the placebo group and the fremanezumab 675-mg sc quarterly group will receive fremanezumab at 675 mg sc as 3 injections (225 mg/1.5 mL) at visit 1 and every 12 weeks thereafter through week 36 (visit 10). For blinding, patients will receive 1 single placebo sc injections at visits 2, 3, 5, 6, 8, and 9.

[redacted]

After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. Patients with CCH will be rolled over from Study TV48125-CNS-30057 until 15 June 2018 as follows (after 15 June 2018 no additional CCH patients will be enrolled):

- Patients who were in the fremanezumab 900-mg iv loading dose group and the fremanezumab 675-mg sc loading dose group will receive fremanezumab at 225 mg as a single sc injection (225 mg/1.5 mL) at visit 1 and every 4 weeks thereafter through week 36 (visit 10). For blinding, these patients will also receive 2 sc placebo injections at visit 1.
- Patients who were in the placebo group will receive a loading dose of fremanezumab at 675 mg as 3 sc injections (225 mg/1.5 mL) at visit 1 and fremanezumab at 225 mg administered as a single sc injection every 4 weeks thereafter through week 36 (visit 10).

[redacted] After 15 June 2018, only patients who participated in

the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

Of note, blinding of the pivotal studies and the initial treatments during this long-term safety extension study will be maintained throughout study participation.

5.1.2. Placebo Investigational Medicinal Product

The placebo will be the same vehicle and excipients as those for fremanezumab. See Table 6 for additional details.

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

As noted in Section 5.1.1.1, as of June 15 2015, CCH patients are no longer enrolling in this study.

Patients who received fremanezumab at 225 mg sc monthly after a loading dose of 900-mg iv or 675 mg sc or fremanezumab at 675 mg sc quarterly during the pivotal studies will continue receiving the same dose (ie, 225 mg sc monthly or 675 mg sc quarterly depending upon their diagnosis and randomization in the pivotal studies) during this long-term safety extension study. These dose regimens are expected to maintain steady state at a blood concentration level that will provide clinical efficacy. The doses and dosing regimens also account for the usual course of the 2 forms of CH; patients with ECH are likely to remit after initial treatment whereas CCH patients are continuously inflicted by pain.

Patients who received placebo during the pivotal studies will be assigned to receive either fremanezumab 675 mg sc quarterly (patients with ECH from Study TV48125-CNS-30056) or a loading dose 675 mg sc followed by monthly fremanezumab at 225 mg sc monthly (patients with CCH from Study TV48125-CNS-30057). This will provide these patients with the opportunity to receive potential benefit from therapeutic doses including the loading dose of 675 mg sc.

In addition to evaluating maintenance of efficacy in this long-term safety extension study, the planned treatments account for the need to adjust treatment duration, which is of particular relevance for ECH. When the cluster cycle is almost over in ECH, the number of headache attacks per day start to decrease with associated mild to moderate intensity. Patients often look for preventive options in the very early part of the headache cycle in an attempt to reduce its duration. Equally, when complete remission is achieved, patients with ECH consider stopping

their medication and thus withdraw from treatment when the cluster period is over (May 2005). Accordingly, continuous long-term treatment in ECH might not be needed as these patients may have long remission periods between the cluster episodes. [redacted]

5.4. Restrictions

Patients will be required to comply with the following restrictions:

5.4.1. Activity

Patients must remain at the investigational center for safety observation for at least 60 minutes after IMP administration. Patients may be asked to remain at the investigational center longer if it is judged to be medically necessary.

5.4.2. 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.

5.4.3. Pregnancy

Restrictions in regard to pregnancy are provided in the inclusion criteria (Section 4.1). Restrictions in regard to sexual activity are also detailed in the inclusion and exclusion criteria (Section 4.1), and contraception methods are reviewed in Appendix E.

In addition, male patients may not donate sperm for the duration of the study and for 7.5 months (approximately 5 half-lives of the active IMP) after administration of the last dose of the IMP.

5.5. Prior and Concomitant Medication or Therapy

Any concomitant medication, treatment, or procedure from the time of consent up to the end of the study, including follow-up, will be recorded on the CRF. Trade name and International Nonproprietary Names (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 drug dictionary.

Patients taking concomitant preventive medications (ie, verapamil, topiramate, valproate, lithium, or methysergide) during the pivotal studies must begin tapering as soon as they begin participation in this study, and they must be off these medications within 1 month from the beginning of participation in this study (not applicable for patients participating in safety follow-up only). See Appendix H for details.

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.

5.6. 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.

5.7. Temporary Discontinuation of Investigational Medicinal Product

Patients who experience CH remission, defined as no CH attacks for 12 successive weeks and 24 successive weeks for patients with ECH and CCH, respectively, at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study) will be offered the possibility to stop treatment. Patients will restart fremanezumab treatment if treatment is stopped and CH attacks resume during the 36-week double blind treatment period. Refer to Section 5.1.1.1 for additional details regarding treatment of these patients. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

5.8. Randomization and Blinding

This is a double-blind study; blinding will be retained from the pivotal studies and throughout this long-term safety extension study. Patients will be assigned to treatments as described in Table 3 and Section 5.1.1.1 based on their randomization in the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057).

5.9. Maintenance of Randomization and Blinding

5.9.1. Maintenance of Randomization

Refer to the protocols for the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) for details regarding randomization of patients in this study.

Packaging vendor(s) will package test IMP and placebo IMP into single-visit kits according to Good Manufacturing Practice (GMP) procedures. Kits will be identical in appearance. Adequate kit supply for upcoming study visits will be managed by interactive response technology (IRT) and kept (refrigerated at 2°C to 8°C) at the investigational centers.

At visits 1 through 10, the IRT will be queried, and investigational center personnel will retrieve and administer each prefilled syringe contained in the appropriately numbered kit(s). Kit numbers will be entered into the CRF.

5.9.2. Blinding and Unblinding

Blinding will be retained from the pivotal studies and throughout this long-term safety extension study.

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).

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

In the event of an emergency, it will be possible to determine which treatment group and dose the patient has been allocated to by accessing the Randomization and Trial Supply Management (RTSM) system. All investigational centers will be provided with details of who can access the system for code breaking at the start of the study. The Medical Monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents.

In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP 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 RTSM system. Breaking of the treatment code can always be performed by the investigator without prior approval of the sponsor; however, the sponsor should be notified that the code was broken, but the patient's IMP assignment should not be revealed to the sponsor. In the event that the RTSM system is not functioning for emergency unblinding, the next course of action is to contact via phone the RTSM 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 in this study.

5.10. Total Blood Volume

The total blood volume to be collected for each patient enrolling in this study for treatment with fremanezumab is approximately 205.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed in Appendix J.

The total blood volume to be collected for each patient enrolling in this for evaluation of ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) is approximately 9 mL.

Details are provided in Appendix L.

6. ASSESSMENT OF EFFICACY

6.1. Assessments of Efficacy

There is no primary efficacy measure.

6.2. 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).

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

6.3. Hospital Anxiety and Depression Scale

The HADS is a validated and reliable, 14-item scale developed 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 at the time points detailed in Table 4. Responses will be recorded in the site tablet.

6.4. 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 at the time points detailed in Table 4. Responses will be recorded in the site tablet.

6.5. 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 at the time points detailed in Table 4. Responses will be recorded in the site tablet.

6.6. 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 at the time points detailed in Table 4. Responses will be recorded in the site tablet.

6.7. 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 4. Responses will be recorded in the 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 ±3 days of the patient's visit if unable to appear at the same time.

6.8. 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 at time points detailed in Table 4. Responses at week 1 will be entered into the electronic diary device, and responses at all other time points will be entered into the site tablet.

6.9. 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."

The PGIC scale will be completed at the time points detailed in Table 4. Responses at week 1 will be entered into the electronic diary device, and responses at all other time points will be entered into the site tablet.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, reported anaphylaxis/hypersensitivity reactions, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight measurements), injection site assessment results, eC-SSRS responses, 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 the 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 or diagnostic 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 the 1st dose of 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 informed consent form (ICF) through the follow-up visit.

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), 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 7):

Table 7: 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: • It does not follow a reasonable temporal sequence from the administration of the IMP. • 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. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
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: • It follows a reasonable temporal sequence from administration of the IMP. • 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. • 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. • It follows a known pattern of response to the IMP.

IMP=investigational medicinal product.

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 end of the follow-up period. Serious adverse events occurring in a patient after the end of the follow-up 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.

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 **al**l of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- ALT or AST increase of ≥3 × the ULN
- total bilirubin increase of ≥2 × 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 Boards (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.

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

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 adverse events of at least moderate severity, events of possible IMP-induced liver injury (AST or ALT ≥3 × the ULN, total bilirubin ≥2 × 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 reactions 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, 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 center 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 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 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 non-compliant 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, transcribed to 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 cessation of treatment with IMP or medical treatment, or further diagnostic workup. (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 4. Clinical laboratory tests will be performed using the central laboratory. However, 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

Serum and urine β-HCG tests will be performed for all WOCBP at time points specified in Table 4. Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting the pregnancy are provided in Section 7.2.

7.5. Physical Examinations

Physical examinations, including weight, will be performed at the time points detailed in Table 4. 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 4. 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 4. 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 investigational centers.

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 investigational center 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 clinically significant (except at the screening visit) 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 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety [adverse events and concomitant medications] only). 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. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the 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 Since Last Visit version will be completed by the patient at every visit, 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 a 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 usage will be monitored throughout the study. Details of prohibited medications are found in Section 5.5.

7.11. Injection Site Assessments

Injection site assessments will be performed immediately (+10 minutes) and 1 hour (±15 minutes) after administration of each dose of the IMP (see Table 4). The injection sites 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 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
- For spontaneous report of local pain after the injection, it will be measured as summarized in Table 8.

Table 8: 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 (±15 minutes) after completion of IMP administration and hourly (±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/ IMMUNOGENICITY/ANCILLARY STUDIES

8.1. Pharmacokinetics Assessment

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

Blood samples [redacted] will be collected via venipuncture/indwelling catheter at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies). 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 all patients will be analyzed for concentration of fremanezumab using a validated method. Details on sample handling, storage, shipment, and analysis are given in Appendix G.

8.2. Pharmacodynamics Assessment

Pharmacodynamics parameters are not evaluated in this study.

8.3. Immunogenicity Testing

Blood samples [redacted] will be collected via venipuncture or indwelling catheter at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety [adverse events and concomitant medications] only) for immunogenicity testing.

Samples from all patients will be analyzed. 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. [redacted]

In preclinical models, CGRP can promote angiogenesis in ischemia, capsaicin-induced synovitis, and neovascularization of tumors. [redacted]

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. [redacted]

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 will be collected from each patient (unless the patient declines testing or local regulations prohibit testing) for pharmacogenomic assessment during the pivotal efficacy study. Pharmacogenomic assessment potentially includes the association analysis of both known and unknown DNA and RNA genetic variations.

8.6. Ancillary Study – Wearable Sensor Substudy

At selected sites, a subset of patients (n=90, approximately 45 from each Phase 3 pivotal study) will be asked to wear a sensor monitoring system (digital wearable device) on the wrist to track sleep patterns and activity patterns. [redacted] After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.

[redacted]

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

There are no statistical considerations for the sample size. Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study

The sample size for each of the pivotal studies TV48125-CNS-30056 for ECH and TV48125-CNS-30057 for CCH is 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately 360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.

Prior to 15 June 2018, patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in StudyTV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all patients who are enrolled in this study for long-term safety evaluation, regardless if they receive study treatment or not.

9.2.2. Safety Analysis Set

The safety analysis set will include all patients who receive any dose of IMP.

9.2.3. Full Analyses Set

[redacted]

9.2.4. Per-Protocol Analysis Set

Not applicable

9.3. Data Handling Conventions

9.3.1. Definition of Baseline

Baseline refers to the run-in period of the pivotal efficacy studies for CH variables and visit 2 (day 0) of the pivotal efficacy studies for all other study variables.

9.3.2. Handling Withdrawals and Missing Data

Missing data will be handled in the same way as in the double-blinded pivotal study. 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 overall and by diagnosis (ECH or CCH headache) and treatment group.

9.4.1. Patient Disposition

Data from patients screened, patients screened but not enrolled and the reason for not being enrolled; patients who are enrolled; patients enrolled but not treated; patients in the ITT, safety, and FASs; 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 ECG findings) will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number of patients [n], mean, standard deviation [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.

9.5. Efficacy Analysis

[redacted]

[redacted]

9.5.1. Primary Endpoint

The primary endpoints for this study are related to safety (Section 2.1). Refer to Section 9.7 for a summary of the safety analyses.

9.5.2. Secondary Endpoints

Not applicable

9.5.3. Exploratory Endpoints

Exploratory efficacy endpoints are as follows:

[redacted]

Wearable sensor substudy exploratory endpoints are the following:

[redacted]

9.5.4. Planned Method of Analysis

The FAS (see Section 9.3) will be used for all efficacy analyses. Summaries will be presented overall and by diagnosis (CCH or ECH) group.

9.5.4.1. Primary Efficacy Analysis

Not applicable

9.5.4.2. Sensitivity Analysis

Not applicable

9.5.4.3. Secondary Efficacy Analysis

Not applicable

9.5.4.4. Exploratory Efficacy Analysis

[redacted]

9.6. Multiple Comparisons and Multiplicity

Not applicable

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 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs, adverse events, and concomitant medications only).

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. Summaries will be presented by treatment group and for all patients. 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 pre-specified boundaries to identify potential 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.

Suicidal ideation and behavior will be measured using the eC-SSRS. Data for patients with positive findings will be listed.

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. Pharmacokinetic Analysis

Pharmacokinetic plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by diagnosis (ECH or CCH) and by treatment group.

In addition, the most appropriate population pharmacokinetic 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. Pharmacokinetics/Pharmacodynamics Analysis

The pharmacokinetics/pharmacodynamics parameters may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy/safety 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 parameters 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. This analysis 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 pharmacokinetic 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 [redacted]. Results will be reported separately.

9.15. Planned Interim Analysis

Not applicable

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, 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 International Council on Harmonization (ICH) Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [CFR] 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, 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 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.

15. REFERENCES

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16. SUMMARY OF CHANGES TO THE PROTOCOL

16.1. Amendment 04 Dated 28 August 2018

The primary reason for this amendment is to describe the way in which patients who participated in the double-blind study for CCH TV48125-CNS-30057 will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.

Prior to 15 June 2018, patients rolled over from the episodic TV48125-CNS-30056 and chronic TV48125-CNS-30057 cluster headache studies into the Long Term Safety study (TV48125-CNS-30058).

As of 15 June 2018, the CCH Study TV48125-CNS-30057 was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. Thus, all CCH patients included in this study have been asked to discontinue treatment and are encouraged to continue in the ADA and safety follow-up portion of this study.

After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.

The Amendment History table has been updated to correct some inadvertent errors.

Updated standardized text has been added to Section 5.9.2.

Additional changes to the protocol are presented below.

Letters of Clarification 05, 06, and 08 and the USM Letter of Clarification have been included. They were inadvertently omitted from being attached to previous protocol amendments. However, all changes to the protocol based on these letters were made at the applicable time points and are noted in the correct amendments. The letters are presented at the end of this amendment.

Letter of Clarification 07 was inadvertently noted and was applicable only to other studies in Sweden (Studies TV48125-CNS-30056 and TV48125-CNS-30057).

Appropriate areas of the protocol have been updated as outlined in the table below.

Original text with changes shown	New wording	Reason/justification for change
Amendment History		
Amendment 03 058 ROW-26 April 2018 ~~186 patients enrolled to date~~ 058 Sweden ~~19 October 2017~~ 07 June 2018 ~~229 patients randomized to date~~	ROW-26 April 2018 Sweden 07 June 2018	To correct amendment dates.
Amendment 02 ROW-03 May 2017 ~~No patients randomized/enrolled to date~~ Sweden-19 October 2017 No patients randomized/enrolled to date	ROW-03 May 2017 Sweden-19 October 2017 No patients randomized/enrolled to date	To correct amendment dates.
Letter of Clarification-USM ROW- 04 April 2018 US - 06 April 2018	ROW- 04 April 2018 US - 06 April 2018	To correct Letter of Clarification dates.
Letter of Clarification 08 ~~20 March 2018~~ 14 March 2018	Letter of Clarification 08 14 March 2018	To correct Letter of Clarification dates.
Letter of Clarification 07 ~~14 March 2018~~ 18 October 2017	Letter of Clarification 07 18 October 2017	Letter of clarification 07 was inadvertently noted and was actually applicable for other studies in Sweden (Studies TV48125-CNS-30056 and TV48125-CNS-30057).
Letter of Clarification 06 ~~19 August 2017~~ 27 August 2017	Letter of Clarification 06 27 August 2017	To correct Letter of Clarification dates.
Synopsis		
Changes made in the body of the protocol are reflected in the synopsis for consistency.		
Section 1.1.3, Study Purpose		
Prior to 15 June 2018, patients rolled over from the episodic TV48125-CNS-30056 and chronic	Prior to 15 June 2018, patients rolled over from the episodic TV48125-CNS-30056 and chronic TV48125-	To describe how patients who participated in the double-blind study for CCH

TV48125-CNS-30057 cluster headache studies into the Long Term Safety study (TV48125 CNS-30058). As of 15 June 2018, CCH Study TV48125-CNS-30057 was terminated based on the study meeting pre specified stopping-criteria (conditional power < 25%) during a planned interim analysis. The planned interim analysis was for futility evaluation based on 50% of patients (ie, the first 150 patients who had completed the study or withdrawn from the study early). An independent unblinded statistician from a third party performed the analysis. The futility evaluation was assessed using conditional power. The sponsor was notified that the conditional power was less than 25% for both comparisons (fremanezumab 900 mg iv loading dose group versus placebo or fremanezumab 675 mg sc loading dose group versus placebo).Thus, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the anti-ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study. As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS -30056) will enroll in this study for active treatment.	CNS-30057 cluster headache studies into the Long Term Safety study (TV48125 CNS-30058). As of 15 June 2018, CCH Study TV48125-CNS-30057 was terminated based on the study meeting pre specified stopping criteria (conditional power < 25%) during a planned interim analysis. The planned interim analysis was for futility evaluation based on 50% of patients (ie, the first 150 patients who had completed the study or withdrawn from the study early). An independent unblinded statistician from a third party performed the analysis. The futility evaluation was assessed using conditional power. The sponsor was notified that the conditional power was less than 25% for both comparisons (fremanezumab 900 mg iv loading dose group versus placebo or fremanezumab 675 mg sc loading dose group versus placebo).Thus, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the anti-ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study. As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment.	(Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 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~~	The clinical pharmacology development (Phase 1) program for fremanezumab in migraine includes 8 completed studies. A total of 318 healthy subjects were enrolled, of which 256 subjects received at least 1 dose of fremanezumab. In 6 of the Phase 1 studies, Studies B0141001, B0141002, B0141006, B0141007, LBR-101-008, and LBR-101-011 [redacted]	To include updated status/information from the Phase 1 development program for fremanezumab.

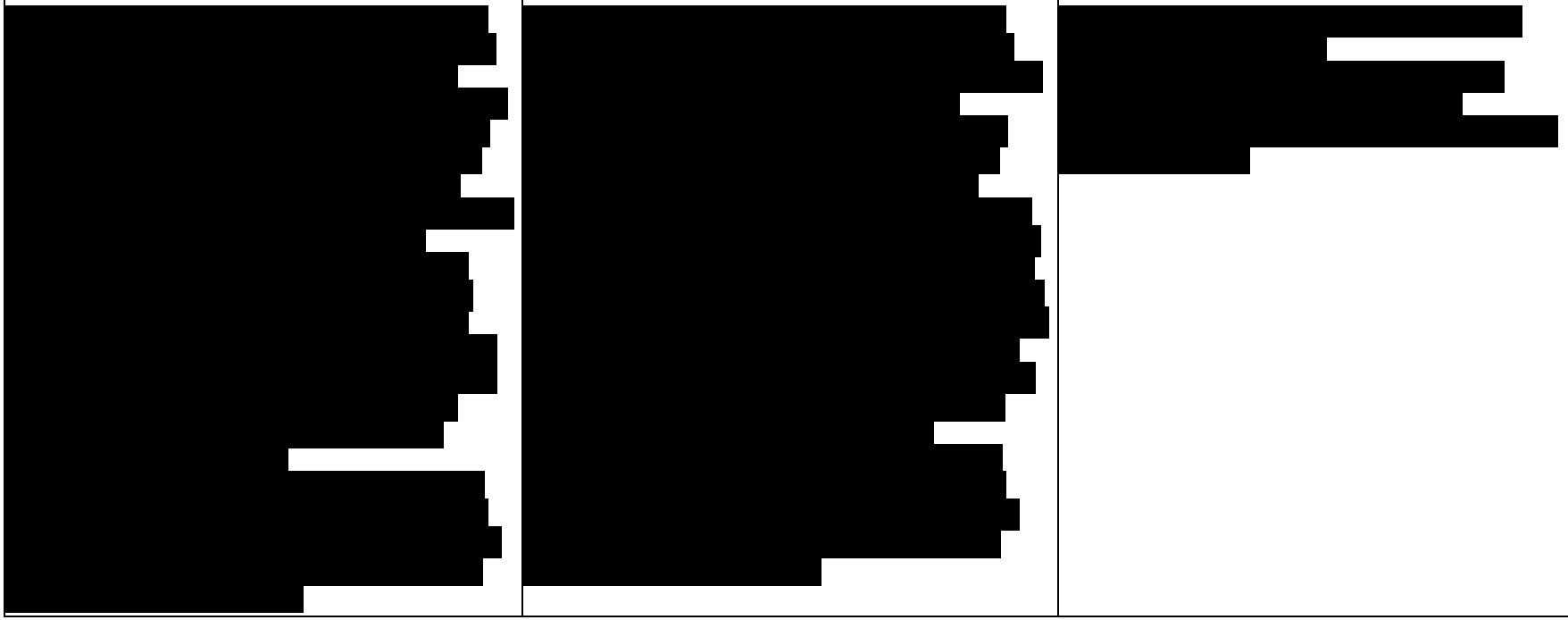
~~acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg 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).~~ The clinical pharmacology development (Phase 1) program for fremanezumab in migraine includes 8 completed studies. A total of 318 healthy subjects were enrolled, 256 subjects received at least 1 dose of fremanezumab. [redacted]. A description of the objectives of these 6 Phase 1 studies is as follows: – Studies B0141001 and B0141002 were iv single-dose-escalation PK and PD studies in healthy men. – Study B0141006 was a 2-cohort, placebo-controlled crossover study to examine the acute effects of iv administration of fremanezumab on capsaicin flare response in healthy men. – Study B0141007 was a parallel-group, repeat-dose PK and PD study of iv administration of fremanezumab in healthy men and women. – Study LBR-101-008 was a single-dose study examining the safety, tolerability, PK, and PD of doses up to 2000 mg administered iv to healthy women.	fremanezumab were analyzed using the original [redacted] A description of the objectives of these 6 Phase 1 studies is as follows: – Studies B0141001 and B0141002 were iv single-dose-escalation PK and PD studies in healthy men. – Study B0141006 was a 2-cohort, placebo-controlled crossover study to examine the acute effects of iv administration of fremanezumab on capsaicin flare response in healthy men. – Study B0141007 was a parallel-group, repeat-dose PK and PD study of iv administration of fremanezumab in healthy men and women. – Study LBR-101-008 was a single-dose study examining the safety, tolerability, PK, and PD of doses up to 2000 mg of fremanezumab administered iv to healthy women. – Study LBR-101-011 was a randomized, placebo-controlled, double-blind, parallel-group study examining the safety, tolerability, absolute bioavailability (BA), and PK of 2 different single doses of fremanezumab administered iv or sc to healthy men and women. Two additional Phase 1 studies, Studies TV48125-PK-10078 and TV48125-BE-10114, were conducted using the current validated bioanalytical method. A description of the objectives of these 2 Phase 1 Studies is as follows: – Study TV48125-PK-10078 was a randomized, double-blind, placebo-controlled study to assess the PK, safety, and tolerability of single-dose sc administration of fremanezumab (single ascending doses and single doses up to 900 mg) in Japanese and Caucasian healthy subjects.	

– Study LBR-101-011 was a randomized, placebo-controlled, double-blind, parallel-group study examining the safety, tolerability, absolute bioavailability (BA), and PK of 2 different single doses of fremanezumab administered iv or sc to healthy men and women. Two additional Phase 1 studies, Studies TV48125-PK-10078 and TV48125-BE-10114, were conducted using the current validated bioanalytical method. A description of the objectives of these 2 Phase 1 Studies is as follows: – Study TV48125-PK-10078 was a randomized, double-blind, placebo-controlled study to assess the PK, safety, and tolerability of single-dose sc administration of fremanezumab (single ascending doses and single doses up to 900 mg) in Japanese and Caucasian healthy subjects. – Study TV48125-BE-10114 was an open-label, single-dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women. – Additional ongoing bioequivalence study (TV48125-BE-10145) is an open-label, single-dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women. [redacted]	Study TV48125-BE-10114 was an open-label, single-dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women. Additional ongoing bioequivalence study (TV48125-BE-10145) is another open-label, single□dose, randomized, parallel, bioequivalence study to compare the PK of fremanezumab administered sc using an auto-injector or a pre-filled syringe in healthy adult men and women. The pharmacokinetics (non-compartmental analysis; Study TV48125-PK-10078) of fremanezumab demonstrated an increase in C_{max} and AUC values slightly greater than the dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values was generally 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-mg 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 $t_{½}$ ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects.	

[redacted] The pharmacokinetics (non-compartmental analysis~~)~~ ; study TV48125-PK-10078) ~~of~~ of fremanezumab demonstrated an increase in Cmax and AUC values slightly greater than the dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values was generally 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-mg 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 $t_{½}$ ranged from 32.2 to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were similar for healthy Japanese and Caucasian subjects. [redacted]		
Section 1.3.1, Known and Potential Benefits and Risks of the Test Investigational Medicinal Product(s)		
Among these events, the following have been identified as adverse drug reactions (identified risks): injection site erythema, injection site rash, injection site induration, and ~~injection site pain~~, injection site pruritus~~, and injection site dermatitis~~. None of these identified risks are	Among these events, the following have been identified as adverse drug reactions (identified risks): injection site erythema, injection site rash, injection site induration, and injection site pruritus. None of these identified risks are considered important risks.	To clarify the identified risks of fremanezumab.

considered important risks.		
Section 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. The benefit and risk assessment for fremanezumab has been re-assessed for patients with CCH. As of 15 June 2018, the CCH study (TV48125-CNS-30057) was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. Thus, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study.	In summary, the benefit and risk assessment for fremanezumab is favorable following review of the outlined data. The benefit and risk assessment for fremanezumab has been re-assessed for patients with CCH. As of 15 June 018, the CCH study (TV48125-CNS-30057) was terminated based on the study meeting pre-specified stopping criteria (conditional power < 25%) during a planned interim analysis. Thus, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 2.1, Primary and Secondary Study Objectives and Endpoints		
As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.	As of 15 June 2018, only patients from the ECH study (Study TV48125-CNS-30056) will enroll in this study for active treatment. As of 15 June 2018, all CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study Data from CCH patients enrolled prior to 15 June 2018 will be evaluated per all objectives of this study.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 3.1, General Design and Study Schematic Diagram		
Prior to 15 June 2018, up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized in Table 3. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057	Prior to 15 June 2018, up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized in Table 3. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled in this study for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.

<table>
<tr><td colspan="3">(planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.</td><td colspan="3">CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.</td><td></td></tr>
<tr><td colspan="7">Section 3.1, General Design and Study Schematic Diagram (Table 3:Summary of Treatments During Study TV48125-CNS-30058)</td></tr>
<tr><td rowspan="3">Study TV48125-CNS-30057 (CCH)
Prior to 15 June 2018 termination of CCH Study TV48125-CNS-30057.
No additional CCH patients will be enrolled after 15 June 2018 for active treatment.</td><td>Fremanezumab 900-mg iv loading dose group</td><td>Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36</td><td rowspan="3">Study TV48125-CNS-30057 (CCH)
Prior to 15 June 2018 termination of CCH Study TV48125-CNS-30057.
No additional CCH patients will be enrolled after 15 June 2018 for active treatment.</td><td>Fremanezumab 900-mg iv loading dose group</td><td>Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36</td><td rowspan="3">To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.</td></tr>
<tr><td>Fremanezumab 675-mg sc loading dose group</td><td>Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36</td><td>Fremanezumab 675-mg sc loading dose group</td><td>Fremanezumab at 225 mg sc monthly (approximately every 4 weeks) through week 36</td></tr>
<tr><td>Placebo group</td><td>Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36</td><td>Placebo group</td><td>Fremanezumab 675-mg sc loading dose followed by monthly (approximately every 4 weeks) fremanezumab at 225 mg sc through week 36</td></tr>
<tr><td colspan="7">Section 3.1, General Design and Study Schematic Diagram</td></tr>
<tr><td colspan="3">Patients with a diagnosis of CCH who experience CH remission, defined as no CH attacks for 24 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping</td><td colspan="3">Patients with a diagnosis of CCH who experience CH remission, defined as no CH attacks for 24 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart fremanezumab</td><td>To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.</td></tr>
</table>

treatment, patients will restart fremanezumab treatment at 225 mg sc monthly through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment with a 675-mg sc loading dose followed by 225-mg sc monthly through week 36. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study.	treatment at 225 mg sc monthly through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab treatment with a 675-mg sc loading dose followed by 225-mg sc monthly through week 36. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study.	
Section 3.1, General Design and Study Schematic Diagram (Figure 1: Overall Study Schematic Diagram)		
Updated to reflect amendment changes.		
Section 3.1, General Design and Study Schematic Diagram: Wearable Sensor Substudy		
		

Section 3.2 Planned Number of Patients and Countries		
Prior to 15 June 2018, up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. After 15 June 2018, only patients who participated in the ECH study **(Study TV48125-CNS-30056)** will be enrolled in this study for active treatment.	Prior to 15 June 2018, up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. After 15 June 2018, only patients who participated in the ECH study **(Study TV48125-CNS-30056)** will be enrolled in this study for active treatment.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 3.3 Justification for Study Design and Selection of Population		
This study is double-blind to ensure impartiality in evaluating the long-term safety and efficacy of different dose regimens of fremanezumab and to avoid unblinding the pivotal studies before they are completed. The blind will be maintained according to standard blinding procedures (see Section 5.9.2) and through the use of dummy injections to ensure that number of injections is the same at each visit for patients with ECH and patients with CCH (see Section 5.1.1.1). After 15 June 2018, only patients who participated in the ECH study **(**Study TV48125-CNS-30056) will be enrolled for active treatment.	This study is double-blind to ensure impartiality in evaluating the long-term safety and efficacy of different dose regimens of fremanezumab and to avoid unblinding the pivotal studies before they are completed. The blind will be maintained according to standard blinding procedures (see Section 5.9.2) and through the use of dummy injections to ensure that number of injections is the same at each visit for patients with ECH and patients with CCH (see Section 5.1.1.1). After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 4.1, Patient Inclusion Criteria		
Criterion C: The patient completes either the Phase 3 pivotal study for ECH (Study TV48125 CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study. Prior to 15 June 2018 patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.	Criterion C: The patient completes either the Phase 3 pivotal study for ECH (Study TV48125 CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study. Prior to 15 June 2018 patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Criterion E: Women of childbearing potential	Criterion E: Women of childbearing potential	Revised to apply to patients participating in safety

(WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP ~~(not applicable for patients participating in safety follow-up only).~~	(WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP	follow-up only.
Section 5.1.1.1, Starting Dose and Dose Levels		
After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. Patients with CCH will be rolled over from Study TV48125-CNS-30057 until 15 June 2018 as follows (after 15 June 2018 no additional CCH patients will be enrolled): Patients who were in the fremanezumab 900-mg iv loading dose group and the fremanezumab 675-mg sc loading dose group will receive fremanezumab at 225 mg as a single sc injection (225 mg/1.5 mL) at visit 1 and every 4 weeks thereafter through week 36 (visit 10). For blinding, these patients will also receive 2 sc placebo injections at visit 1. Patients who were in the placebo group will receive a loading dose of fremanezumab at 675 mg as 3 sc injections (225 mg/1.5 mL) at visit 1 and fremanezumab at 225 mg administered as a single sc injection every 4 weeks thereafter through week 36 (visit 10). [redacted]	After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. Patients with CCH will be rolled over from Study TV48125-CNS-30057 until 15 June 2018 as follows (after 15 June 2018 no additional CCH patients will be enrolled): Patients who were in the fremanezumab 900-mg iv loading dose group and the fremanezumab 675-mg sc loading dose group will receive fremanezumab at 225 mg as a single sc injection (225 mg/1.5 mL) at visit 1 and every 4 weeks thereafter through week 36 (visit 10). For blinding, these patients will also receive 2 sc placebo injections at visit 1. Patients who were in the placebo group will receive a loading dose of fremanezumab at 675 mg as 3 sc injections (225 mg/1.5 mL) at visit 1 and fremanezumab at 225 mg administered as a single sc injection every 4 weeks thereafter through week 36 (visit 10). [redacted]	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.

[redacted] After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	[redacted] After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	
Section 5.7, Temporary Discontinuation of Investigational Medicinal Product		
Patients who experience CH remission, defined as no CH attacks for 12 successive weeks and 24 successive weeks for patients with ECH and CCH, respectively, at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study) will be offered the possibility to stop treatment. Patients will restart fremanezumab treatment if treatment is stopped and CH attacks resume during the 36-week double blind treatment period. Refer to Section 5.1.1.1 for additional details regarding treatment of these patients. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.	Patients who experience CH remission, defined as no CH attacks for 12 successive weeks and 24 successive weeks for patients with ECH and CCH, respectively, at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study) will be offered the possibility to stop treatment. Patients will restart fremanezumab treatment if treatment is stopped and CH attacks resume during the 36-week double blind treatment period. Refer to Section 5.1.1.1 for additional details regarding treatment of these patients. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment.	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.
Section 5.9.2, Blinding and Unblinding		
In the event of an emergency, it will be possible to determine which treatment group and dose the patient has been allocated to by accessing the Randomization and Trial Supply Management (RTSM) system. All investigational centers will be provided with details of who can access the system	In the event of an emergency, it will be possible to determine which treatment group and dose the patient has been allocated to by accessing the Randomization and Trial Supply Management (RTSM) system. All investigational centers will be provided with details of who can access the system for code breaking at the	New standardized text.

for code breaking at the start of the study. The Medical Monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents. In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP ~~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 RTSM system. Breaking of the treatment code can always be performed by the investigator without prior approval of the sponsor; however, the sponsor should be notified that the code was broken, but the patient's IMP assignment should not be revealed to the sponsor. ~~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.~~	start of the study. The Medical Monitor or equivalent should be notified following unblinding. Any unblinding of the IMP performed by the investigator must be recorded in the source documents. In case of a serious adverse event, pregnancy, or in cases when knowledge of the IMP 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 RTSM system. Breaking of the treatment code can always be performed by the investigator without prior approval of the sponsor; however, the sponsor should be notified that the code was broken, but the patient's IMP assignment should not be revealed to the sponsor.	
Section 7.8, Immunogenicity		
Blood samples for serum ADA assessment will be collected at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety [adverse events and concomitant medications] only). 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. After 15 June 2018, only patients who participated in the	Blood samples for serum ADA assessment will be collected at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety [adverse events and concomitant medications] only). 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. After 15 June 2018, only patients who participated in the	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.

ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. All CCH patients included in this study have been asked to discontinue treatment, and are encouraged to continue in the ADA and safety follow-up portion of this study. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	
Section 8.6, Ancillary Study – Wearable Sensor Substudy		
[redacted]	[redacted]	[redacted]
Section 9.1, Sample Size and Power Considerations		
There are no statistical considerations for the sample size. Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. The sample size for each of the pivotal studies	There are no statistical considerations for the sample size. Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. The sample size for each of the pivotal studies	To describe how patients who participated in the double-blind study for CCH (Study TV48125-CNS-30057) will continue to participate in this Long Term Safety study (Study TV48125-CNS-30058), since the CCH study has been terminated.

TV48125-CNS-30056 for ECH and TV48125-CNS-30057 for CCH is 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long term safety study. Approximately 360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP. Prior to 15 June 2018 patients from the ECH study and the CCH study were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	TV48125-CNS-30056 for ECH and TV48125-CNS-30057 for CCH is 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long term safety study. Approximately 360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP. Prior to 15 June 2018 patients from the ECH study and the CCH TV48125 studies were enrolled. After 15 June 2018, only patients who participated in the ECH study (Study TV48125-CNS-30056) will be enrolled for active treatment. At the time of unblinding the treatment code in Study TV48125-CNS-30057 (planned for Q4 2018), those CCH patients who were receiving placebo in Study TV48125-CNS-30057 (ie, never received any study drug) will not be required to complete additional safety follow-up visits, and will be discharged from the study.	
Section 9.10, Pharmacokinetics/Pharmacodynamics Analysis		
The pharmacokinetics/pharmacodynamics parameters may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy/safety response(s).	The pharmacokinetics/pharmacodynamics parameters may be estimated by compartmental techniques. The pharmacokinetics parameters will be based on fremanezumab measurements. The pharmacodynamics parameters will be the efficacy/safety response(s).	Clarification of use of PK/PD data.
Appendix A Clinical Laboratories and Other Departments and Institutions		
[redacted]	[redacted]	Updated name and contact information for Sponsor's contact point.

[redacted]	[redacted]	
[redacted]	[redacted]	Updated telephone number for Dr. Kessler

16.1.1. Letter of Clarification 05 Dated 10 May 2017

LETTER OF CLARIFICATION 05

Study number: TV48125-CNS-30058

Clinical Study Protocol

TV48125-CNS-30058 A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache
IND number: 129606
EudraCT number: 2016-003172-43
Original Protocol : 08/08/2016 Amendment #1 Approval 30/Nov/2016 Amendment #2 Approval 03/May/2017

May 10th, 2017

Dear Investigator,

The purpose of this letter of clarification is to clarify that Pharmacogenomics samples will be taken only during studies TV48125-CNS-30056 and TV48125-CNS-30057 and will not be collected in study TV48125-CNS-30058.

Current wording	Proposed wording	Rationale
Protocol Synopsis: The long-term 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 assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. 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, satisfaction with treatment, and health status. In addition, blood will be collected for pharmacokinetics, immunogenicity, biomarker~~, and pharmacogenomics~~ **(pharmacogenomics is collected**	**Protocol Synopsis:** The long-term 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 assessments, assessments for anaphylaxis and hypersensitivity, and administration of the eC-SSRS. 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, satisfaction with treatment, and health status. In addition, blood will be collected for pharmacokinetics, immunogenicity, biomarker **(pharmacogenomics is collected during the pivotal studies,** unless not allowed per local regulation)	Clarifying that Pharmacogenomics samples will not be collected during TV48125-CNS-30058, but only during the pivotal studies.

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during the pivotal studies, unless not allowed per local regulation) ~~**analyses,**~~ and urine will be collected for biomarker analysis.	and urine will be collected for biomarker analysis.	
APPENDIX P. EXPLORATORY BIOMARKERS SAMPLES Blood samples (total of 17.0 mL; 6 mL for plasma, 8.5 mL for serum, and 2.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 4 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**~~ **should** be collected ~~**at baseline (or a later visit)**~~ **during the pivotal studies** 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. Data will be kept confidential and stored separately. 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.	**APPENDIX P. EXPLORATORY BIOMARKERS SAMPLES** Blood samples (total of 17.0 mL; 6 mL for plasma, 8.5 mL for serum, and 2.5 mL for RNA [PAXgene]) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 4 for serum, plasma, and RNA biomarker measures. Urine will be collected in parallel with blood collection. In addition, a 6-mL whole blood sample **should** be collected **during the pivotal studies** 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. Data will be kept confidential and stored separately. 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.	Clarifying that Pharmacogenomics samples will not be collected during TV48125-CNS-30058, but only during the pivotal studies.

These clarifications are **not considered substantial** and will be incorporated to the protocol during the next substantial amendment. 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] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

Signature [redacted]

Name: [redacted]

2

Title Senior Director, Migraine and Headache Clinical Development
Department Clinical Development, Teva Pharmaceuticals

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16.1.2. Letter of Clarification 06 Dated 27 August 2017 to Correct a Typographical Error in Sweden Protocol Amendment 02

LETTER OF CLARIFICATION 06
Studies TV48125-CNS-30056 / TV48125-CNS-30057/ TV48125-CNS-30058

Clinical Study Protocols

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
IND number: 129606
EudraCT number: 2016-003278-42
Date: 08/08/2016 Amendment #2 Approval 01/May/2-17

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
IND number: 129606
EudraCT number: 2016-003171-21
Date: 08/08/2016 Amendment #2 Approval 01/May/2-17

TV48125-CNS-30058 A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache
IND number: 129606
EudraCT number: 2016-003172-43
Date: 08/08/2016 Amendment #2 Approval 03/May/2017

Teva Pharmaceuticals

August 27th, 2017

Dear Investigator

The purpose of this letter of clarification is to correct a typo inadvertently included in the header of section 16.1 of protocols TV48125-CNS-30057 and TV48125-CNS-30058 as well as in the rescreening paragraph of TV48125-CNS-30056.

Current wording	Proposed wording	Rational
Protocol TV48125-CNS-30058 Section 16- Summary of Changes to the Protocol/ 16.1 - Amendment 02 Dated 03 May 2017 (table header) ~~**Placebo-Controlled Study-Episodic**~~ **Uncontrolled Study** Cluster Headache Study TV48125-CNS-30058	**Protocol TV48125-CNS-30058** Section 16- Summary of Changes to the Protocol/ 16.1 - Amendment 02 Dated 03 May 2017 (table header) **Uncontrolled Study** Cluster Headache	Typo correction
Protocol TV48125-CNS-30057 Section 16- Summary of Changes to the Protocol/ 16.1 - Amendment 02 Dated 01 May 2017(table header) Placebo-Controlled Study-~~**Episodic**~~ **Chronic** Cluster Headache Study TV48125-CNS-30057	**Protocol TV48125-CNS-30057** Section 16- Summary of Changes to the Protocol/ 16.1 - Amendment 02 Dated 01 May 2017 (table header) Placebo-Controlled Study **Chronic** Cluster Headache STUDY TV48125-CNS-30057	Typo correction
Protocol TV48125-CNS-30057 Section 16- Summary of Changes to the Protocol 16.1 - Amendment 02 Dated 01 May 2017 (table section appendix H PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS) Concomitant Medications Allowed and Disallowed Steroids: The only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use. Butalbital: Screening/run-in period: Disallowed if used more	**Protocol TV48125-CNS-30057** Section 16- Summary of Changes to the Protocol 16.1 - Amendment 02 Dated 01 May 2017 (table section appendix H PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS) Concomitant Medications Allowed and Disallowed Steroids: The only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use. Butalbital: Screening/run-in period: Disallowed if used more than 10 days during the screening/run-in period.	Typo correction

than 3 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 4 days during the screening/run-in period. Patients can use opioids PRN after randomization into the study.	Patients can use butalbital as needed (PRN) after randomization into the study. Opioids: Screening/run-in period: Disallowed if used more than 15days during the screening/run-in period. Patients can use opioids PRN after randomization into the study.	
Protocol TV48125-CNS-30056 Section 4.5 Rescreening A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again, except for patients who do not meet study inclusion criterion "b" "i" of the required number of cluster attacks during run-in period. These patients may be eligible for one additional rescreening if approved by the sponsor on a case-by-case basis.	**Protocol TV48125-CNS-30056** Section 4.5 Rescreening A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again, except for patients who do not meet study inclusion criterion "i" of the required number of cluster attacks during run-in period. These patients may be eligible for one additional rescreening if approved by the sponsor on a case-by-case basis.	Typo correction

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 Linor Haimson (Linor.Haimson@teva.co.il) or Luxiane-Lea Belzus (Luxiane-Lea.Belzus@teva.co.il) if you have any questions or concerns regarding this letter.

Sincerely,

Signature [redacted]

Name: [redacted]

Title: [redacted]

Department: Clinical Development, Teva Pharmaceuticals

Teva Pharmaceuticals

16.1.3. Letter of Clarification 07 Dated 18 October 2017.

Letter of clarification 07 was inadvertently noted and was actually applicable for other studies in Sweden (Studies TV48125-CNS-30056 and TV48125-CNS-30057).

LETTER OF CLARIFICATION 07 FOR SWEDEN ONLY ADDENDUM TO GLOBAL PROTOCOL AMENDMENT 2

Study number: TV48125-CNS-30057

Clinical Study Protocol

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
IND number: 129606
EudraCT number: 2016-003171-21
Original Protocol: 08 August 2016 Amendment #1 Approval: 30 November 2016 Amendment #2 Approval: 01 May 2017

18 October 2017

Dear Investigator,

The purpose of this addendum is to clarify that in Sweden incorrectly randomized patients will always be withdrawn from the study.

Current wording with additions shown in bold	**Proposed wording**	**Rationale**
4.3.Withdrawal Criteria and Procedures: 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. [1] Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.	**4.3.Withdrawal Criteria and Procedures:** 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.[1] Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate.	This update has been made in agreement with the Swedish Medicinal Product Agency to clarify that in Sweden incorrectly randomized patients will always be withdrawn from the study.

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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. [1] In Sweden, incorrectly randomized patients are always withdrawn from the study.	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. [1] In Sweden, incorrectly randomized patients are always withdrawn from the study.	

These changes will be incorporated to the global protocol during the next amendment, as applicable. Please ensure that this addendum is maintained with the study protocol. Also, please provide a copy of this addendum to your IRB/IEC for review and acknowledgement.

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

Sincerely,

[redacted]

Signature

Name: [redacted]

Title: [redacted]

Department Clinical Development, Teva Pharmaceuticals

Teva Pharmaceuticals 41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | www.tevapharm-na.com

16.1.4. Letter of Clarification 08 Dated 14 March 2018

LETTER OF CLARIFICATION 08

Studies TV48125-CNS-30056 / TV48125-CNS-30057/ TV48125-CNS-30058

Clinical Study Protocols

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
IND number: 129606
EudraCT number: 2016-003278-42
Date: 08/August/2016 Amendment #2; Approval 01/May/2017

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
IND number: 129606
EudraCT number: 2016-003171-21
Date: 08/August /2016 Amendment #2; Approval 01/May/2017

TV48125-CNS-30058: A Multicenter, Double-Blind, Double-Dummy Study to Explore the Long-Term Safety and Efficacy of TEV-48125 for the Prevention of Cluster Headache
IND number: 129606
EudraCT number: 2016-003172-43
Date: 08/August /2016 Amendment #2; Approval 03/May/2017

Page 1 of 3

March 14th, 2018

Dear Investigator,

The purpose of this letter of clarification is:

1. To extend the study duration of protocol TV48125-CNS-30056 by approximately 1 year (no change to the individual treatment period per patient)
2. To extend the study duration of protocol TV48125-CNS-30057 by approximately 1quarter (no change to the individual treatment period per patient)
3. To extend the study duration of protocol TV48125-CNS-30058 by approximately 2 quarters (no change to the individual treatment period per patient)
4. To clarify that triple ECG is not required at visit 8 of protocol TV48125-CNS-30058

Current wording	Proposed wording	Rationale
TV48125-CNS-30056 **Planned Study Period:** Q4/2016 (first patient in) to Q2/2018 (last patient last visit) **Study Duration:** 21 months from Q4/2016 to Q2/2018	TV48125-CNS-30056 **Planned Study Period:** Q4/2016 to **Q2/2019** **Study Duration:** approximately **33** months from Q4/2016 to **Q2/2019**	The study recruitment rate is lower than initially expected. Extension of the study period is needed in order to meet the number of patients planned for this protocol.
TV48125-CNS-30057 **Planned Study Period:** Q4/2016 (first patient in) to Q3/2018 (last patient last visit) **Study Duration**: Approximately 24 months from Q4/2016 to Q3/2018	TV48125-CNS-30057 **Planned Study Period:** Q4/2016 to **Q4/2018** **Study Duration**: approximately **27** months from Q4/2016 to **Q4/2018**	The study recruitment rate is lower than initially expected. Extension of the study period is needed in order to meet the number of patients planned for this protocol.
TV48125-CNS-30058 **Planned Study Period:** Q1/2017 (first patient in) to Q4/2019 (last patient last visit) **Study Duration:** Approximately 36 months from Q1/2017 to Q4/2019	TV48125-CNS-30058 **Planned Study Period:** Q1/2017 to **Q2/2020** **Study Duration:** Approximately **42** months from Q1/2017 to **Q2/2020**	The study recruitment rate is lower than initially expected. Extension of the study period is needed in order to meet the number of patients planned for this protocol.

16.1.5. Letter of Clarification USM Dated 06 April 2016

Pharmaceutical Industries Ltd.

[redacted]

April 6, 2018

Dear Investigator,

This note-to-file is a clarification pertaining to the handling of concomitant preventative medications used in studies 30056 and 30057 in the event of enrollment of 30056 and 30057 study patients into the long-term safety study (LTSS) 30058.

As you recall, a maximum of two concomitant preventative medications are allowed in Studies 30056 and 30057, but none in the LTSS 30058. Based on feedback from some of you related to my previous communication of March 20, 2018, Teva has decided to prepare a protocol amendment to study LTSS 30058 to better clarify how those patients on concomitant preventative medications entering into study LTSS 30058 should be treated. The main substantive change that *will be effective immediately* will be to require tapering of all concomitant preventive medications used in the pivotal studies (verapamil, topiramate, valproate, lithium and methysergide) for a period of time that should not exceed 1 month after enrollment into study LTSS 30058 to avoid any potential safety concerns with abrupt discontinuation of these concomitant preventive medications.

Also, all patients who satisfactorily complete studies 30056 or 30057, may be offered to enroll in the treatment arm of the LTSS (Study 30058), independent of the concomitant preventative medications listed above, as currently allowed in the protocol. Patients in the treatment arm of the LTSS who restart preventive medication, will have to discontinue participation in the LTSS per the current protocol; such cases will be treated as Important Protocol Deviations.

We anticipate formalizing the protocol amendment in Teva as soon as possible for submission to the IRB for approval. In the interim, the tapering of the concomitant preventive medications (except for verapamil) prior to enrollment into study LTSS 30058 should be handled as a protocol deviation. Because it is a protocol deviation, it will require documentation and notification of your IRB.

Thank you for your continued support and commitment to the Cluster Program.

Sincerely,

Signature [redacted]

Name: [redacted]

[redacted]

[redacted]

Teva Pharmaceuticals

16.2. Amendment 03 Dated 26 April 2018

The primary reason for this amendment is to provide clarification on concomitant preventive medications allowed in the treatment arm of this long-term safety study (Study TV48125-CNS-30058). Patients who satisfactorily complete pivotal double-blind studies TV48125-CNS-30056 or TV48125-CNS-30057 may be offered the opportunity to enroll in Study 30058 either for treatment or for ADA safety follow-up, independent of their concomitant preventive medications (ie, verapamil, topiramate, valproate, lithium, or methysergide). For those continuing to receive active treatment, tapering of all concomitant preventive medications used in the pivotal studies will be required, which is in line with clinical practice. Tapering will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in Study 30058 to avoid any potential safety concerns with abrupt discontinuation of these concomitant preventive medications.

Patients in the treatment arm of Study 30058 who restart preventive medication will have to discontinue participation in the study per the current protocol; such cases will be treated as important protocol deviations. No other exceptions to the protocol will be permitted.

The number of patients who will be offered the opportunity to roll over into the treatment arm has been increased: approximately 360 patients may roll over for treatment. The overall sample size of the entire 30058 study will not change and will remain at 600 patients. Consequently, the number of patients who may roll over for ADA and safety follow-up only is correspondingly decreased: approximately 240 patients may roll over for ADA and safety follow-up. The justification behind this change is driven from the natural history of patients with chronic CH, which is characterized as less than 1 attack-free month in 1 year. Therefore, these patients want and have a necessity to continue treatment. This change will offer these patients the opportunity to roll over into the treatment arm.

Additionally, the duration of the study has been extended by 6 months because the study recruitment rate into Studies 30056 and 30057 has been lower than initially expected. The duration will be approximately 42 months, from Q1/2017 to Q2/2020**.** Extension of the study period is needed in order to meet the number of patients planned for this protocol. There is no change to the individual treatment period per patient. There is also no change to the procedures for patients in the study.

It has been clarified that pharmacogenomics samples are taken only during the pivotal studies and will not be collected in Study 30058.

The assessment "Perform triplicate 12-lead ECGs" at visit 8 (week 28 ± 3 days) has been deleted from Appendix B. It was mistakenly added and does not align with Table 4, Study Procedures and Assessments for Treated Patients, which schedules triplicate 12-lead ECGs at weeks 12, 24, 36, and 40/ end-of-study visit.

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.

Original text with changes shown	New wording	Reason/justification for change
Synopsis		
Changes made in the body of the protocol are reflected in the synopsis for consistency.		
Investigator Agreement page, Sponsor's Authorize Representative.		
[redacted]	[redacted]	Change of personnel at Teva.
Coordinating Investigator Agreement page		
[redacted]	[redacted]	Full contact information added.
Section 3.1, General Design and Study Schematic Diagram		
Up to ~~300~~ 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized inTable 3.	Up to 360 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized inTable 3.	This change will offer additional patients the opportunity to roll over into the treatment arm and continue treatment with fremanezumab.
The study duration will be for approximately ~~36~~ 42 months, from Q1/2017 to ~~Q4/2019~~ Q2/2020.	The study duration will be for approximately 42 months, from Q1/2017 to Q2/2020.	Extension of the study period is needed in order to meet the number of patients planned for this protocol.
Section 3.2, Planned Number of Patients and Countries		
The study is expected to start in Q1/2017 (first patient in) and last until approximately ~~Q4/2019~~ Q2/2020 (last patient last visit)	The study is expected to start in Q1/2017 (first patient in) and last until approximately Q2/2020 (last patient last visit)	Extension of the study period is needed in order to meet the number of patients planned for this protocol.

Original text with changes shown	New wording	Reason/justification for change
Section 3.3, Justification for Study Design and Selection of Population		
Concomitant medications that are commonly prescribed for the preventive treatment of CH (listed in Appendix H) are prohibited throughout this study so that effects of the test IMP can be distinguished from effects of these concomitant preventive medications. Thus, patients who were taking concomitant preventive medications (up to 2) during the pivotal studies will be required to ~~stop taking~~ taper off these medications during the first month of treatment in this study.	Concomitant medications that are commonly prescribed for the preventive treatment of CH (listed in Appendix H) are prohibited throughout this study so that effects of the test IMP can be distinguished from effects of these concomitant preventive medications. Thus, patients who were taking concomitant preventive medications (up to 2~~)~~ during the pivotal studies will be required to taper off these medications during the first month of treatment in this study.	Tapering of all concomitant preventive medications used in the pivotal studies will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in Study 30058 to avoid any potential safety concerns with abrupt discontinuation of these concomitant preventive medications.
Section 4.1, Patient Inclusion Criteria		
f. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH (ie, verapamil, topiramate, valproate, lithium, or methysergide) for the duration of this study. (~~Note~~: Patients ~~taking verapamil during the pivotal studies~~ must begin tapering ~~verapamil~~ these preventive medications as soon as they ~~enroll~~ begin participation ~~in~~ in this study, ~~and they must~~. The period of time needed to taper off these medications will be ~~off verapamil within~~ based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study [Appendix H) (not applicable for patients participating in safety follow-up only).	f. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH (ie, verapamil, topiramate, valproate, lithium, or methysergide) for the duration of this study. Patients must begin tapering these preventive medications as soon as they begin participation in this study. The period of time needed to taper off these medications will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study (Appendix H) (not applicable for patients participating in safety follow-up only).	Appropriate tapering of these concomitant preventive medications can avoid risks to patients and mitigate causing adverse health effects.
Section 4.3, Withdrawal Criteria and Procedures for the Patient		
In the event that a patient was incorrectly ~~randomized~~ enrolled 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.	In the event that a patient was incorrectly enrolled 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.	Clarification. Blinding will be retained from the pivotal studies.

Original text with changes shown	New wording	Reason/justification for change
Section 5.5, Prior and Concomitant Medication or Therapy		
Patients taking concomitant preventive medications (ie, verapamil, topiramate, valproate, lithium, or methysergide) during the pivotal studies must begin tapering ~~verapamil~~ as soon as they enroll in this study, and they must be off ~~verapamil~~ these medications within 1 month from the beginning of participation in the study (not applicable for patients participating in safety follow-up only). ~~All other medications that are commonly prescribed for the preventative treatment of CH and systemic steroids are prohibited throughout the double-blind treatment period of this long-term safety extension stud~~	Patients taking concomitant preventive medications (ie, verapamil, topiramate, valproate, lithium, or methysergide) during the pivotal studies must begin tapering these preventive medications as soon as they enroll in this study, and they must be off these medications within 1 month from the beginning of participation in this study (not applicable for patients participating in safety follow-up only).	Appropriate tapering of these concomitant preventive medications can avoid risks to patients and mitigate causing adverse health effects.
Section 9.1, Sample Size and Power Considerations		
All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately ~~300~~360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately ~~300~~ 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.	All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately 360 patients (out of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 240 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.	This change will offer additional patients the opportunity to roll over into the treatment arm and continue treatment with fremanezumab.
Appendix A, Clinical Laboratories and Other Departments and Institutions		
Sponsor's Authorized Representative		

[redacted]	[redacted]	Change of personnel at Teva**.**
Legal Representative of the Sponsor in the European Union		
[redacted]	[redacted]	Change of personnel at Teva.

Sponsor's Representative of Global Patient Safety and Pharmacovigilance		
[redacted]	[redacted]	Change of personnel at Teva.
Pharmacogenomics/Biomarker Evaluation		
[redacted]	[redacted]	Change of personnel at Teva
Appendix B, Visit 8 (Week 28 ± 3 Days)		
~~Perform triplicate 12-lead ECGs~~		Mistakenly added and does not align with schedule of assessments.

Appendix H: Preventive Cluster Headache Medications and Disallowed Medications		
The following medications will be considered as being used for the prevention of cluster headache attacks regardless of the initial indication ~~and are disallowed during the double-blind treatment period of this long-term extension study~~:	The following medications will be considered as being used for the prevention of cluster headache attacks regardless of the initial indication:	Patients treated in the pivotal studies with any of the concomitant preventive medications listed in the protocol (verapamil, lithium, methysergide, valproate, topiramate) as a concomitant preventive medication or for other indication must start tapering as soon as they begin this study. The period of time needed to taper off from any concomitant preventive medication will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study. Appropriate tapering of these concomitant preventive medications can avoid risks to patients and mitigate causing adverse health effects.
Patients ~~treated with verapamil as a concomitant preventive medication or other indication in the pivotal studies~~ must start tapering ~~verapamil~~these preventive medications as soon as they begin this study. The period of time needed to taper off ~~verapamil~~ these medications will be based on the investigator's medical judgment but should not exceed 1 month ~~of~~ from the beginning of participation in this study.	Patients must start tapering these preventive medications as soon as they begin this study. The period of time needed to taper off these medications will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study.	Tapering of all concomitant preventive medications used in the pivotal studies will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in Study 30058 to avoid any potential safety concerns with abrupt discontinuation of these concomitant preventive medications.
Appendix P, Exploratory Biomarkers Samples		
[redacted]	[redacted]	[redacted]

16.3. Amendment 02 Dated 03 May 2017

The primary reason for this amendment is to provide clarification on feedback from participating investigators and regulatory agencies and to incorporate nonsubstantial changes to maintain alignment with the protocols with protocol Amendment 02 for Studies TV48125-CNS-30056 and TV48125-CNS-30057. 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 4 (Study Procedures and Assessments for Patients Enrolling in the Study from the Pivotal Efficacy Studies) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect the changes described below.

Original text with changes shown	New wording	Reason/justification for change
Section 1.2.1, Nonclinical Studies		
Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP) ~~via the iv and sc routes of administration with once-weekly dosing for up to 6 months~~.	Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP).	Revised for clarification.
[redacted]		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 ~~150~~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.	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.	Added updated information for nonclinical studies.
Section 1.2.2, Clinical Studies		
In addition, there are ~~5~~4 ongoing clinical studies of fremanezumab: 2 pivotal efficacy studies in patients with migraine (1 study each	In addition, there are 5 ongoing clinical studies of fremanezumab: 2 pivotal efficacy studies in patients with migraine (1 study each for	Added updated information for clinical

Original text with changes shown	New wording	Reason/justification for change
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); ~~and~~ 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.~~)~~.	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.	studies.
Section 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 ~~Completed studies~~ included 2 single-ascending-dose pharmacokinetic~~s~~ and pharmacodynamic~~s~~ 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~~comparing~~ the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011). [redacted] 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 [redacted]	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). [redacted] 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 [redacted] results are described below. The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C_{max} and AUC values	Added updated information for pharmacology studies.

Original text with changes shown	New wording	Reason/justification for change
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- [redacted] maximum observed concentration (t_{max}) values was generally [redacted] to 7 days post sc doses~~.0 hours postdose after a 1-hour~~ [redacted] Mean values for apparent total volume of distribution during the terminal phase (V_z/F) ~~the V_{ss}~~ after a single sc~~iv~~ dose ranged from 5.7 to [redacted] 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[redacted] to 0.0895 mL/min~~276 L/day~~ at this dose range. The mean $t_{½}$ ranged from 32.2 [redacted] -to 36.2 days. Fremanezumab exposure parameters and overall pharmacokinetic profile were ~~2000 mg. Absolute bioavailability of the sc dose was~~ similar for healthy Japanese and Caucasian subjects. Comparison of exposure parameters (C_{max} and $AUC_{0-\infty}$) [redacted] from Studies LBR-101-011 and TV48125-PK-10078 at the 225- and 900-mg sc dose levels indicate a 2.9- [redacted]	slightly greater than dose proportionality over the sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values was generally 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 $t_{½}$ 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- 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 sample analysis.	
Section 1.2.2.2, Clinical Safety and Efficacy Studies		
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 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	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 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-	Updated for clarification.

Original text with changes shown	New wording	Reason/justification for change
TV48125-CNS-30049 and TV48125 CNS-30050, as of 23 April 2016).	CNS-30049 and TV48125 CNS-30050, as of 23 April 2016).	
Section 2.2.1, Exploratory Objectives and Endpoints (other section affected by this change: Section 3.1, General Design and Study Schematic Diagram; and Section 9.5.3, Exploratory Endpoints)		
• [redacted]	• [redacted]	Edited exploratory objective for clarity.
Section 3.1, General Design and Study Schematic Diagram (other sections affected by this change: Protocol Title, Section 3.5, Table 5: Study Procedures and Assessments for Patients Rolling Over from the Pivotal Efficacy Studies for Evaluation of Antidrug Antibodies and Safety [Adverse Events and Concomitant Medications] Only; Section 4.1, Patient Inclusion Criteria; Section 7.8, Immunogenicity; Section 8.3, Immunogenicity Testing; Appendix B, Study Procedures and Assessments by Visit)		
This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).	This is a 68-week extension study to evaluate the long-term safety and efficacy of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed (PRN).	Revised for clarification
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 this study protocol 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-CNS-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 ~~Up to~~ 300 eligible~~Female and male patients with CCH and ECH who complete the pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) may enter this long-term safety study if they provide informed consent and meet the inclusion/exclusion criteria. In addition, patients who do not complete the pivotal efficacy studies, and patients who complete the pivotal efficacy studies but do not wish to continue treatment during this long-term safety study, may enroll in this study for the purpose of evaluating ADAs, fremanezumab concentrations, and safety (adverse events and concomitant medications) approximately~~	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 this study protocol) 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-CNS-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 Up to 300 eligible patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125 CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized in Table 3.	Updated for clarification.

Original text with changes shown	New wording	Reason/justification for change
~~7.5 months after administration of the last dose of the IMP.~~ ~~Eligible~~ patients with ECH and CCH rolling over from the pivotal studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057, respectively) will receive fremanezumab during this study, as summarized in Table 3.		
All patients will return to the investigational center approximately every 4 weeks after administration of the first dose of the IMP (visit 1 [week 0]) through the end-of-treatment (EOT) visit (visit 11 [week 40]), which will occur approximately 4 weeks after administration of the last~~final~~ dose of the IMP (week 36). Patients will return for a follow-up visit (visit 12) to evaluate ADAs, ~~fremanezumab concentrations,~~ biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of the IMP. ~~This visit is for the purpose of evaluating ADAs, fremanezumab concentrations, biomarkers, and safety only~~. Patients who withdraw from the study before completing the 40-week treatment period will have EOT visit procedures and assessments performed on the last day the patients received the IMP or as soon as possible thereafter, and they will be asked to return for a follow-up visit approximately 7.5 weeks after their last dose of IMP. Patients who enter the long-term safety follow-up study for safety follow-up only will not follow the same visit schedule as that for patients receiving treatment. The procedures and assessments for the patients participating in the safety follow-up are described in Table 5.	All patients will return to the investigational center approximately every 4 weeks after administration of the first dose of the IMP (visit 1 [week 0]) through the end-of-treatment (EOT) visit (visit 11 [week 40]), which will occur approximately 4 weeks after administration of the last dose of the IMP (week 36). Patients will return for a follow-up visit (visit 12) to evaluate ADAs, biomarkers, and safety (adverse events and concomitant medications) approximately 7.5 months after the last dose of the IMP. Patients who withdraw from the study before completing the 40-week treatment period will have EOT visit procedures and assessments performed on the last day the patients received the IMP or as soon as possible thereafter, and they will be asked to return for a follow-up visit approximately 7.5 weeks after their last dose of IMP. Patients who enter the long-term safety follow-up study for safety follow-up only will not follow the same visit schedule as that for patients receiving treatment. The procedures and assessments for the patients participating in the safety follow-up are described in Table 5.	Updated for clarification.
Section 3.1, General Design and Study Schematic Diagram, Table 3 (footnotes a and b)		
a.In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30056, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of ~~either~~ test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visits 1, 4, 7, and 10, and a single sc injection of test IMP or placebo IMP at visits 2, 3, 5, 6, 8, and 9. b. In order to maintain blinding throughout the study, the number	a.In order to maintain blinding throughout the study, the number of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30056, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visits 1, 4, 7, and 10, and a single sc injection of test IMP or placebo IMP at visits 2, 3, 5, 6, 8, and 9. b. In order to maintain blinding throughout the study, the number of	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
of sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30057, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of either test IMP (1.5-~~-~~mL-~~ ~~injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visit 1, and patients will receive a single sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) at all other visits.	sc injections at each visit will be the same for all patients rolling over from Study TV48125-CNS-30057, regardless of their assigned treatment group. Thus, patients will receive 3 sc injections of either test IMP (1.5-mL injections each containing fremanezumab at a concentration of 150 mg/mL) or 1 sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) and 2 sc injections of placebo IMP (1.5-mL injections) at visit 1, and patients will receive a single sc injection of test IMP (1.5-mL injection containing fremanezumab at a concentration of 150 mg/mL) at all other visits.	
Section 3.2, Planned Number of Patients and Countries (other section affected by this change: Section 3.1, General Study Design and Study Schematic Diagram and Figure 1: Overall Study Schematic Diagram [table note]; and Section 9.1, Sample Size and Power Considerations)		
~~Approximately 300~~ Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.	Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study.	Revised text to reflect that all subjects will have the opportunity to participate in either the long-term treatment and long-term safety follow-up or the long-term safety follow-up only.
Section 3.4, Stopping Rules for the Study (other section affected by this change: Section 4.3, Withdrawal Criteria and Procedures for the Patient)		
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 Appendix C~~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 Appendix C, noncompliance, or adverse event).	Added clarification that lack of efficacy may result in withdrawal from the study.
Section 3.5, Schedule of Study Procedures and Assessments, Table 4: Study Procedure and Assessments for Treated Patients		
Table 4: Study Procedures and Assessments for Treated Patients ~~Enrolling in the Study from the Pivotal Efficacy Studies~~	**Table 4: Study Procedures and Assessments for Treated Patients**	Table title revised for clarification.
Section 3.5, Schedule of Study Procedures and Assessments, Table 4: Study Procedure and Assessments for Treated Patients (footnote q; other section affected by this change: Appendix B, Study Procedures and Assessments by Visit)		
q. Blood samples for pharmacokinetic analysis will be collected prior to dosing, where applicable. Patients who ~~are participating in~~signed consent for the wearable sensor substudy (at the pivotal studies) only will return to the investigational center for up to 2 additional visits after any dose of the IMP for blood sampling for pharmacokinetics analysis, triplicate12-lead ECGs, and inquiries about adverse events and	q. Blood samples for pharmacokinetic analysis will be collected prior to dosing, where applicable. Patients who signed consent for the wearable sensor substudy (at the pivotal studies) only will return to the investigational center for up to 2 additional visits after any dose of the IMP for blood sampling for pharmacokinetics analysis, triplicate12-lead ECGs, and inquiries about adverse events and concomitant medications. These visits	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
concomitant medications. These visits should occur during the following time periods relative to any dose of the IMP: 3 to 10 days or 15 to 20 days after IMP.	should occur during the following time periods relative to any dose of the IMP: 3 to 10 days or 15 to 20 days after IMP.	
Section 3.5, Schedule of Study Procedures and Assessments, Table 5: Study Procedures and Assessments for Patients Rolling Over from the Pivotal Efficacy Studies for Evaluation of Antidrug Antibodies and Safety (Adverse Events and Concomitant Medications) Only (other section affected by this change: Section 7.11, Injection Site Assessments; and Appendix B, Study Procedures and Assessments by Visit).		
Procedures and assessments Removed "Blood sample for pharmacokinetic analysis" row from table		Revised for correctness.
Section 4, Selection and Withdrawal of Patients (other section affected by this change: Appendix C, Quality Control and Quality Assurance)		
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.	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.
Section 4.1, Patient Inclusion Criteria (other section affected by this change: Section 5.5, Prior and Concomitant Medication or Therapy)		
Patients may be ~~enrolled~~ included in the treatment portion of the ~~this~~ study only if they meet all of the following criteria:	Patients may be included in the treatment portion of the study only if they meet all of the following criteria:	Revised for clarification.
a. The patient is a male or female and 18 to 70 years of age, inclusive, at the start of the pivotal study.	a. The patient is a male or female and 18 to 70 years of age, inclusive, at the start of the pivotal study.	Revised for clarification.
c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study.	c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance and at least 75% diary data completion during the pivotal study.	Revised for clarification.
d. Women may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at visit 1; are sterile or postmenopausal; and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.	d. Women may be included only if they have a negative beta-human chorionic gonadotropin (β-HCG) test at visit 1, are sterile or postmenopausal, and are not lactating (not applicable for patients participating in safety follow-up only). Definitions of sterile and postmenopausal are given in Appendix E.	Revised for clarification.
e. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP (not applicable for patients participating in safety follow-up only).	e. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods (see Appendix E) for the duration of the study and for 7.5 months after discontinuation of IMP (not applicable for patients participating in safety follow-up only).	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
f. 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 administration of IMP (not applicable for patients participating in safety follow-up only).	f. 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 administration of IMP (not applicable for patients participating in safety follow-up only).	Revised for clarification.
g. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH for the duration of this study. (Note: Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation [Appendix H]) (not applicable for patients participating in safety follow-up only).	g. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH for the duration of this study. (Note: Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation [Appendix H]) (not applicable for patients participating in safety follow-up only).	Revised for clarification.
h. 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 (not applicable for patients participating in safety follow-up only).	h. 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 (not applicable for patients participating in safety follow-up only).	Revised for clarification.
Section 4.2, Patient Exclusion Criteria (other section affected by this change: Section 5.5, Prior and Concomitant Medication or Therapy)		
Patients will be excluded from participating in the treatment portion of~~not be randomized/enrolled in~~ this study if they meet any of the following criteria: a. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.	Patients will be excluded from participating in the treatment portion of this study if they meet any of the following criteria: a. The patient has a history of any suicide attempt in the past or current active suicidal ideation, as measured by the eC-SSRS.	Revised for clarification.
Patients rolling over only for safety follow up and ADA who are not receiving study medication are not required to fulfil all inclusion exclusion criteria.	Patients rolling over only for safety follow up and ADA who are not receiving study medication are not required to fulfil all inclusion exclusion criteria.	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
Section 4.3, Withdrawal Criteria and Procedures for the Patient (other section affected by this change: Appendix C, Quality Control and Quality Assurance)		
8. Investigator may discontinue an individual patient from the study at any time for any reason, such as 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.	8. Investigator may discontinue an individual patient from the study at any time for any reason, such as 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 inAppendix J.	Added text for clarification.
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.	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.	Added text for clarification.
Section 4.5, Rescreening		
A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again.	A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again.	New section added.
Section 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.	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.	New section added.
Section 5.1.1, Test Investigational Medicinal Product		
Fremanezumab is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor.	Fremanezumab is a fully humanized IgG2a/kappa monoclonal antibody derived from a murine precursor.	Revised for clarification.
Section 5.9.2, Blinding and Unblinding		
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.	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.	Added text for clarification.
Section 6.2, Electronic Diary Device		
~~Exploratory efficacy~~Efficacy endpoints related to CH attacks will be derived from data collected daily ~~during the double-blind treatment period~~ using an electronic diary device. Eligible patients will receive comprehensive training at screening from the	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.	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
investigational ~~center~~site personnel on the use of the electronic diary device ~~at screening during the pivotal studies~~. Investigational ~~center~~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. ~~On each day, the patient will be asked to record real-time diary data regarding the CH attacks.~~ 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.~~use) in real time or retrospectively for the previous 24-hour period~~. Patients will be asked about their performance at work or at school on CH attack-free days. Additional details ~~regarding the questions patients will answer~~ 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 ~~that~~ no more than ~~48 hours~~2 days have elapsed since completion of that day. If more than ~~48 hours~~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	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 use) in real time or retrospectively for the previous 24-hour period. 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	
Section 7.1.8, Protocol Deviations Because of an Adverse Event (other sections affected by this change: Section 4, Selection and Withdrawal of Patients; Section 7.3, Medication Error and Special Situations Related to the Investigational Medicinal Products; and Appendix C, Quality Control and Quality Assurance)		

Original text with changes shown	New wording	Reason/justification for change
If a patient experiences an adverse event or medical emergency, deviations from the protocol may be warranted to~~allowed on a case by case basis. To~~ ensure patient safety. ~~a~~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.	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.	Revised for clarification.
Section 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. A non-compliant patient may continue taking the study treatment only if this does not jeopardize the patient's safety	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. A non-compliant patient may continue taking the study treatment only if this does not jeopardize the patient's safety	Revised for clarification.
Section 7.4.1, Serum Chemistry, Hematology, and Urinalysis		
Clinical laboratory tests (serum chemistry, hematology, and ~~coagulation,~~ urinalysis) will be performed at the time points detailed in Table 4. Clinical laboratory tests will be performed using the central laboratory. However, 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.	Clinical laboratory tests (serum chemistry, hematology, and urinalysis) will be performed at the time points detailed in Table 4. Clinical laboratory tests will be performed using the central laboratory. However, 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.	Revised for clarification.
Section 7.8, Immunogenicity		
Blood samples for serum ADA assessment will be collected at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety ~~[~~, ~~fremanezumab concentrations,~~ adverse events~~,~~ and concomitant	Blood samples for serum ADA assessment will be collected at the time points detailed in Table 4 (patients enrolling in this study from the pivotal efficacy studies) and Table 5 (patients rolling over from the pivotal efficacy studies for evaluation of ADAs and safety [adverse events and concomitant medications] only). Blood samples	Text added to clarify the procedure in the event of anaphylaxis occurrence.

Original text with changes shown	New wording	Reason/justification for change
medications] only). 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.	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.	
Section 7.11, Injection Site Assessments (other sections affected by this change: Section 3.5, Schedule of Study Procedures and Assessments, Table 4: Study Procedure and Assessments for Treated Patients(footnote x and Appendix B, Study Procedures and Assessments by Visit)		
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~~, and pain~~. Severity will be graded according to the following criteria: • Injection site erythema, induration, and ecchymosis will be graded according to measurements: absent, 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site. • For spontaneous report of local pain after the injection, it~~Injection site pain~~ will be measured as summarized in Table 8~~5~~.	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: • Injection site erythema, induration, and ecchymosis will be graded according to measurements: absent, 5 to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site. • For spontaneous report of local pain after the injection, it will be measured as summarized in Table 8.	Added clarification for injection site assessment windows.
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 (±15 minutes) after completion of IMP administration and hourly (±15 minutes) thereafter until the reaction is of moderate or less severity.	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 (±15 minutes) after completion of IMP administration and hourly (±15 minutes) thereafter until the reaction is of moderate or less severity.	Added visit windows for clarification.
Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) should~~will also~~ be recorded as adverse events.	Injection-site reactions (injection site erythema, induration, ecchymosis, and pain) should be recorded as adverse events.	Added for clarification.
Section 9.1, Sample Size and Power Considerations		
There are no statistical considerations for the sample size. ~~A total of approximately 300~~Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. ~~All patients will receive (sc) fremanezumab during this study.~~ The sample size for each of the pivotal studies TV48125-CNS-30056 for ECH and TV48125 CNS-30057 for CCH is 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately 300 patients (out	There are no statistical considerations for the sample size. Up to 600 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. The sample size for each of the pivotal studies TV48125-CNS-30056 for ECH and TV48125 CNS-30057 for CCH is 300 patients. All of the 600 patients participating in the pivotal studies will roll over to the long-term safety study. Approximately 300 patients (out of the completers from the pivotal studies) will be offered to receive	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
of the completers from the pivotal studies) will be offered to receive treatment during 40 weeks and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 300 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.	treatment during 40 weeks, and these patients will return for a follow-up visit approximately 7.5 months after the last dose of the IMP. Approximately 300 patients (including early termination patients in the pivotal studies) will be offered to continue in a long-term safety evaluation collecting AEs, SAEs, and for ADA evaluation approximately 7.5 months after administration of the last dose of the IMP.	
Appendix E, Women of Childbearing Potential and Birth Control Methods		
Women of non-childbearing potential are defined as: • notSurgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • One 1-year postmenopausal (stable amenorrhea no menses for 12 months without alternative medical cause plus highincreased concentration of follicle-stimulating hormone, (FSH) serum level in the postmenopausal range of more than 2335 U/L) in women not using hormonal contraception or hormonal replacement therapy • 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.	**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 serum level 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 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.	Revised for clarification.
• Bilateral tubal occlusion and • vVasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.	• Bilateral tubal occlusion • Vasectomized partner provided that he is the sole sexual partner and has received medical assessment of the surgical process.	Revised for clarification.
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)be contacted by the investigational center.	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).	Revised for clarification.
Appendix G, Handling, Labeling, Storage, and Accountability for Investigational Medicinal Product(s)		
Preparation instructions for subcutaneous (sc) injections:	Preparation instructions for subcutaneous (sc) injections:	Revised for correctness.

Original text with changes shown	New wording	Reason/justification for change
Investigational medicinal product (IMP) should be allowed to equilibrate at room temperature for ~~15~~45 to ~~30~~60 minutes before sc administration.	Investigational medicinal product (IMP) should be allowed to equilibrate at room temperature for 45 to 60 minutes before sc administration.	
Appendix H, Preventive Cluster Headache Medications and Disallowed Medications		
~~Note that intra-articular steroid injections, steroid ear drops, steroids for ocular use, and steroid creams for topical use are permitted during the study.~~Note that the only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use.	Note that the only allowed steroids are intra-articular injection or ocular, ear drops, intranasal, inhaled, and creams for topical use.	Revised for clarification.
Appendix L, Total Blood Volume (other sections affected by this change: Section 3.5, Schedule of Study Procedures and Assessments, Table 4: Study Procedure and Assessments for Treated Patients [footnote s]; Section 5.10, Total Blood Volume; Appendix B, Study Procedures and Assessments by Visit; and Appendix P, Exploratory Biomarkers Samples)		
Total blood volume to be collected for each patient in this study is approximately ~~185.5~~205.5 mL for scheduled tests.	Total blood volume to be collected for each patient in this study is approximately 205.5 mL for scheduled tests.	Revised for clarification.
Serum chemistry sample volume was revised from 3 mL to 3.5 mL Serum pregnancy sample volume was revised from 3 mL to 3.5 mL and number of samples was changed from 4 to 1 Hematology sample volume was revised from 3 mL to 2 mL Coagulation sample of 4.5 mL (4 samples in total) was added Number of pharmacokinetic samples was revised from up to 13 to 13 Biomarker serum sample volume was revised from 14.5 mL to 8.5 mL	Serum chemistry: 3.5 mL at 4 time points Serum pregnancy: 3.5 mL at 1 time point Hematology: 2 mL at 4 time points Coagulation: 4.5 mL at 4 time points Pharmacokinetics: 4 mL at 13 time points Biomarker serum: 8.5 mL at 5 time points	Revised for clarification.
[redacted]	[redacted]	Revised for clarification.
[redacted]	[redacted]	Revised for clarification.
Appendix N, Pharmacokinetics Samples (other section affected by this change: Appendix O, Immunogenicity Samples)		
Separated plasma will be transferred in approximately equal portions in 2 labeled 2-mL polypropylene tubes (Sets A and B).	Separated plasma will be transferred in approximately equal portions in 2 labeled 2-mL polypropylene tubes (Sets A and B).	Revised for clarification.
Set A samples will be transported frozen, with a temperature data	Set A samples will be transported frozen, with a temperature data	Revised for clarification.

Original text with changes shown	New wording	Reason/justification for change
logger and with dry ice sufficient for 4 days, on a monthly basis ~~by next day courier~~ to the central laboratory~~ or bioanalytical laboratory~~. Set B samples will be sent ~~either~~ to the same laboratory as that for Set A ~~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)~~. Instructions as to the disposition of the Set B samples will be provided by the sponsor.	logger and with dry ice sufficient for 4 days, on a monthly basis to the central laboratory. 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.	

16.4. Amendment 01 Dated 30 November 2016

The primary reason for this amendment is to incorporate nonsubstantial changes to maintain alignment with the protocols with protocol Amendment 01 for Studies TV48125-CNS-30056 and TV48125-CNS-30057. 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 4 (Study Procedures and Assessments for Patients Enrolling in the Study from the Pivotal Efficacy Studies) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect the changes described below.

Original text with changes shown	New wording	Reason/justification for change
Global change (except for protocol title)		
fremanezumab~~TEV-48125~~	fremanezumab	Generic name will now be used rather than the Teva-assigned number.
Section 2.2.2, Wearable Sensor Substudy Exploratory Objectives and Endpoints (other section affected by the change: Section 9.5.3, Exploratory Endpoints)		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/justification for change
and sleep efficiency and headache intensity during CH 		
Section 3.1, General Design and Study Schematic Diagram		
This is a 68-week extension study to evaluate the long-term safety of fremanezumab~~TEV-48125~~ in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.	This is a 68-week extension study to evaluate the long-term safety of fremanezumab in adult patients with CH. During the course of any CH attack, patients will be allowed to use acute medications to treat acute headaches, as needed.	Added sentence to emphasize/clarify that acute medications are allowed.
Section 3.1, General Design and Study Schematic Diagram (other section affected by this change: Section 5.1.1.1 Starting Dose and Dose Levels		
Patients with a diagnosis of ECH who experience CH remission, defined as no CH attacks for 12 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart treatment at their previous dose regimen through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment, patients will restart fremanezumab~~TEV-48125~~ treatment at 675 mg sc	Patients with a diagnosis of ECH who experience CH remission, defined as no CH attacks for 12 successive weeks at any time after starting IMP (ie, administration of the first dose of IMP in the pivotal study), will be offered the possibility to stop treatment and continue to attend the subsequent scheduled visits. If treatment is stopped and CH attacks resume within 12 weeks after stopping treatment, patients will restart treatment at their previous dose regimen through week 36. If treatment is stopped and CH attacks resume after more than 12 weeks after stopping treatment,	Specified that patients who experience remission will have the option to either continue taking IMP or to discontinue taking IMP. Clarified that patients who elect to discontinue taking the IMP will be required to continue to attend study visits after stopping

Original text with changes shown	New wording	Reason/justification for change
[redacted]	[redacted]	treatment with the IMP.
Section 3.2, Planned Number of Patients and Countries		
Approximately 300 patients from ~~342 patients with CH are expected to complete~~ the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study; ~~274 of these patients (182 patients who received TEV-48125 during the Phase 3 pivotal efficacy studies and 92 patients who received placebo during the Phase 3 pivotal efficacy studies) are anticipated to enroll in this study, and 192 of these patients are anticipated to complete this study~~. The study is planned to be conducted in approximately 12~~15~~ countries in approximately 80~~60~~ investigational centers. The study is expected to start in Q1/2017 and last until approximately Q4/2019.	Approximately 300 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll 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 Q1/2017 and last until approximately Q4/2019	Updated the number of patients based on characteristics of CH (typical durations of cluster periods, etc). The numbers of investigational centers and countries were updated to align with the numbers in for the pivotal studies.
Section 3.4, Stopping Rules for the Study		
The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol ~~violation or~~ deviation as defined in Appendix C, noncompliance, or adverse event).	The investigator and/or sponsor can withdraw a patient from the study at any time for any reason (eg, protocol deviation as defined in Appendix C, noncompliance, or adverse event).	Change to terminology (violation changed to deviation) to align with guidance from the ICH.
Section 4.1, Patient Inclusion Criteria		
c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient safety and patient compliance~~major~~	c. The patient completes either the Phase 3 pivotal study for ECH (Study TV48125-CNS-30056) or the Phase 3 pivotal study for CCH (Study TV48125-CNS-30057) without important protocol deviations related to patient	Change to terminology (violation changed to deviation) to align with guidance from the ICH.

Original text with changes shown	New wording	Reason/justification for change
~~protocol violations~~.	safety and patient compliance.	The types of important protocol deviations that are exclusionary are now specified for clarity.
g. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH for the duration of this study. (Note: Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation [Appendix H].)	g. The patient must be willing to stop concomitant medications used in clinical practice for the prevention of CH for the duration of this study. (Note: Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation [Appendix H].)	For safety reasons, verapamil should be tapered.
Section 5.1.1.1, Starting Dose and Dose Levels		
Of note, blinding of the pivotal studies and the initial treatments during this long-term safety extension study will be maintained throughout study participation.	Of note, blinding of the pivotal studies and the initial treatments during this long-term safety extension study will be maintained throughout study participation.	Added to clarify this point.
Section 5.3.1, Justification for Dose of Test Investigational Medicinal Product		
[redacted]	[redacted]	Update made to reflect the option for patients who experience CH remission to either continue or discontinue taking the IMP.
Section 5.5, Prior and Concomitant Medication or Therapy		
Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation. All other m~~M~~edications that are commonly prescribed for the preventive treatment of CH and systemic steroids are prohibited throughout the double-blind treatment period of this long-term safety extension study. See Appendix H for details.	Patients taking verapamil during the pivotal studies must begin tapering verapamil as soon as they enroll in this study, and they must be off verapamil within 1 month of beginning study participation. All other medications that are commonly prescribed for the preventive treatment of CH and systemic steroids are prohibited throughout the double-blind treatment period of this long-term safety extension study. See Appendix H for details.	For safety reasons, verapamil should be tapered.
Section 5.7, Temporary Discontinuation of Investigational Medicinal Product		
Patients who experience CH remission, defined as no CH attacks for	Patients who experience CH remission, defined as no CH	Update made to reflect the

Original text with changes shown	New wording	Reason/justification for change
[redacted]	[redacted]	option for patients who experience CH remission to either continue or discontinue taking the IMP.
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)		
The total blood volume to be collected for each patient enrolling in this study for treatment with fremanezumab~~TEV-48125~~ is approximately 18~~20~~5.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed in Appendix J.	The total blood volume to be collected for each patient enrolling in this study for treatment with fremanezumab is approximately 185.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed 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 5 PAXGene RNA samples are to be collected, the total blood volume is reduced by 20 mL. This text was also updated to clarify that additional blood may be collected in the case of elevated liver function tests as detailed in Appendix J.
Section 6.2, Electronic Diary Device		
If a patient fails to complete the diary for the preceding day ~~within the allowed timeframe (ie, by 1200 on the latter day)~~, the patient will be prompted to enter the missed day's information the next time he/she accesses the electronic diary provided that 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 the diary information for that day~~missed day's information~~, 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 that 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.
Section 6.8, Patient-Perceived Satisfactory Improvement (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)		
The PPSI was developed by ten Klooster et al (2006) ~~and is composed of an unmarked 100-mm visual analog scale~~for ~~Pain~~	The PPSI was developed by ten Klooster et al (2006) for pain intensity and was adjusted for CH symptoms	In the e-diary, a VAS cannot be used.

Original text with changes shown	New wording	Reason/justification for change
~~Intensity (VAS-PI) with "no pain" and "unbearable pain" as anchors and a question regarding change in~~ pain intensity and was adjusted for CH symptoms improvement. Patients will mark the level of CH-associated pain ~~on the VAS-PI~~ and indicate if pain is "much worse," "moderately worse," "slightly worse," "unchanged," "~~unsatisfactory~~slightly improved," "~~satisfactory~~moderately improved," or "~~good to very good~~much improved" compared with ~~baseline (visit 2 [day 0] of the Phase 3 pivotal efficacy studies)~~4 weeks ago. PPSI will be defined as the change in pain ~~on the VAS-PI~~that corresponds with a minimal rating of "~~satisfactory~~slightly improved."	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."	Understanding that CH causes pain, the report to measure improvement or not is adapted for CH.
Section 6.9, 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~~how they feel now~~ compared with how they felt ~~before receiving IMP~~at the start of the study (the time after the patient received the first IMP dose) ~~on a 7-point scale, where 1 is~~as "much worse," "moderately worse," "slightly worse," "stayed the same," "a little better," "moderately better," or "much better."~~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.~~"	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."	Updated the text to align with the e-diary.
Section 7.1.3, Severity of an Adverse Event		
For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), refer to Section 7.11.	For severity grading of local tolerability (injection site erythema, induration, ecchymosis, and pain), refer to Section 7.11.	Added reference to Section 7.11 to clarify how local tolerability findings will be graded.

Original text with changes shown	New wording	Reason/justification for change
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)		
Any administration of IMP that is not in accordance with the study protocol should be reported ~~on the CRF either~~ as an important deviation~~violation~~, if it meets the important deviation~~violation~~ 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 ~~violation~~ deviation criteria, all instances of incorrect IMP administration should be ~~categorized~~reported in the clinical trial management system.~~on the CRF as "Non-Compliance to IMP."~~	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), 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 categorized in the clinical trial management system.	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 deviation information.
Section 7.8, Immunogenicity		
Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction and~~(eg, anaphylaxis)~~.	Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction and anaphylaxis.	Correction to align with the rest of the protocol.
Section 7.9, Assessment of Suicidality		
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, ~~score ≥4 for suicidal ideation and/or a suicide attempt. If the patient scores a 4 for suicidal ideation, then the investigator~~ 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~~the~~ patient reports current suicide ideation with specific plan and intent~~scores a 5 for suicidal ideation and/or there is a suicide attempt~~, 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.	A positive finding will be defined as 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.	Adapted text to the eC-SSRS electronic questionnaire format.
Section 7.11, Injection Site Assessments (other section affected by this change: Section 3.5, Schedule of Procedures and Assessments)		
Injection site assessments will be performed immediately (+ 10 minutes) and 1 hour after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain.~~; and~~ ~~s~~Severity will be graded according to the following criteria:	Injection site assessments will be performed immediately (+ 10 minutes) and 1 hour after receiving each dose of the IMP. The injection site(s) will be assessed for erythema, induration, ecchymosis, and pain. ~~S~~everity will be graded according to the following criteria:	Deleted grade 4 to align severity grading with severity scale for adverse events.

<table>
<tr><th>Original text with changes shown</th><th>New wording</th><th>Reason/justification for change</th></tr>
<tr><td>
Injection-site erythema, ~~injection-site~~ induration, and ~~injection-site~~ ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
…
<table>
<tr><td>Symptom</td><td>Severity ~~G~~grade</td><td>Assessment</td></tr>
<tr><td rowspan="5">Pain</td><td>0</td><td>Absent~~No pain~~</td></tr>
<tr><td>1 (mild)</td><td>Painful on touch~~Mild~~</td></tr>
<tr><td>2 (moderate)</td><td>Pain on ambulation~~Moderate~~</td></tr>
<tr><td>3 (severe)</td><td>Spontaneously painful~~Severe~~</td></tr>
<tr><td>~~4~~</td><td>~~Worst possible~~</td></tr>
</table>
If a patient has severe injection site induration, erythema, ~~and/or~~ ecchymosis, ~~and/~~or ~~grade 3 (severe) or grade 4 (worst possible) injection site~~ pain at 1 hour after completion of ~~the~~ IMP administration, the patient will be reassessed at 3 hours after completion of~~receiving the~~ IMP administration and hourly thereafter until the reaction~~/pain~~ 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) will also be recorded as adverse events~~ as described in Section 7.1~~.
</td><td>
Injection-site erythema, induration, and ecchymosis will be graded according to measurements: absent, 5 mm to ≤50 mm (mild), >50 to ≤100 mm (moderate), and >100 mm (severe). Induration must be assessed by careful superficial palpation avoiding pressuring or squeezing the injection site.
…
<table>
<tr><th>Symptom</th><th>Severity grade</th><th>Assessment</th></tr>
<tr><td rowspan="4">Pain</td><td>0</td><td>Absent</td></tr>
<tr><td>1 (mild)</td><td>Painful on touch</td></tr>
<tr><td>2 (moderate)</td><td>Pain on ambulation</td></tr>
<tr><td>3 (severe)</td><td>Spontaneously painful</td></tr>
</table>
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.
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) will also be recorded as adverse events.
</td><td></td></tr>
<tr><td colspan="3">Section 8.6, Ancillary Studies – Wearable Sensor Substudy
[redacted]</td></tr>
</table>

Original text with changes shown	New wording	Reason/justification for change
[redacted]	[redacted]	
Section 9.1, Sample Size and Power Considerations		
There are no statistical considerations for the sample size. A total of approximately 300 patients from~~342 patients with CH are expected to complete~~ the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study; ~~274 of these patients (182 patients who received TEV-48125 during the Phase 3 pivotal efficacy studies and 92 patients who received placebo during the Phase 3 pivotal efficacy studies) are anticipated to enroll in this study, and 192 of these patients are anticipated to complete this study~~. All patients will receive (sc) fremanezumab~~TEV-48125~~ during this study.	There are no statistical considerations for the sample size. A total of approximately 300 patients from the Phase 3 pivotal efficacy studies (Studies TV48125-CNS-30056 and TV48125-CNS-30057) are expected to enroll in this study. All patients will receive (sc) fremanezumab during this study.	Updated the number of patients based on characteristics of CH (typical durations of cluster periods, etc).
Section 10, Quality Control and Quality Assurance		
This includes information about protocol amendments, deviations ~~and violations~~, 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.
Appendix B, Study Procedures and Assessments by Visit		
Edit in each instance of the following: Perform local injection site assessment immediately (+ 10 minutes) and at 1 hour (±15 minutes) after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection site reaction~~ and/or injection site pain~~.	Perform local injection site assessment immediately (+ 10 minutes) and at 1 hour (±15 minutes) after completing IMP administration. Additional injection site assessments may be performed based on the severity of any observed injection site reaction.	To align with changes in Section 7.11.
Week 1 (Day 7) Patients will complete the Patient Global Impression of Change	Week 1 (Day 7) Patients will complete the Patient Global Impression of	To align with changes in Section 6.8.

Original text with changes shown	New wording	Reason/justification for change
(PGIC) scale and the Patient Perceive Satisfactory Improvement (PPSI) ~~(complete the Visual Analog Scale for Pain Intensity [VAS-PI] and respond to question about change in pain intensity)~~ at 1 week after receiving IMP using the electronic diary device.	Change (PGIC) scale and the Patient Perceive Satisfactory Improvement (PPSI) at 1 week after receiving IMP using the electronic diary device.	
Edit in each instance of the following: • Complete the PPSI ~~(complete the VAS-PI and respond to question about change in pain intensity)~~.	Edit in each instance of the following: • Complete the PPSI.	To align with changes in Section 6.8.
Edit in each instance of the following: • Obtain ~~a~~an 1~~4~~8.5-mL blood sample (6 mL each for serum and plasma and 2~~6~~.5 mL for RNA) for biomarker analysis.	Edit in each instance of the following: • Obtain a 14.5-mL blood sample (6 mL each for serum and plasma and 2.5 mL for RNA) for biomarker analysis.	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.
Added at visit 10 • Perform triplicate 12-lead ECGs.	• Perform triplicate 12-lead ECGs.	To align with the schedule of procedures and assessments for patients enrolling in the study from the pivotal efficacy studies.
Appendix H, Preventive Cluster Headache Medications and Disallowed Medications		
Patients treated with verapamil as a concomitant preventive medication or other indication in the pivotal studies must start tapering verapamil as soon as they begin this study. The period of time needed to taper off verapamil will be based on the investigator's medical judgment but should not exceed 1 month.	Patients treated with verapamil as a concomitant preventive medication or other indication in the pivotal studies must start tapering verapamil as soon as they begin this study. The period of time needed to taper off verapamil will be based on the investigator's medical judgment but should not exceed 1 month.	For safety reasons, verapamil should be tapered.
Appendix N, Pharmacokinetics Samples (other section affected by this change: Appendix O, Immunogenicity 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.	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.
Appendix P, Exploratory Biomarkers Samples		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/justification for change
		[redacted]

ADA=antidrug antibody; CCH=chronic cluster headache; CH=cluster headache; CRF=case report form; eC-SSRS= electronic Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ECH=episodic cluster headache; ICH=International Council on Harmonisation; IMP=investigational medicinal product; PGIC=Patient Global Impression of Change; PPSI=Patient-Perceived Satisfactory Improvement; sc=subcutaneous; RNA=ribonucleic acid; VAS=visual analog scale; VAS-PI-visual analog scale for pain intensity

16.5. 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

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
IND number: 129606
EudraCT number: 2016-003278-42
Final Protocol Date:08/08/2016 Amendment #1 Approval 30 Nov 2016

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
IND number: 129606
EudraCT number: 2016-003171-21
Date: 08/08/2016 Amendment #1 Approval 30 Nov 2016

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
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
Appendix E: WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS Women of childbearing potential are defined as: • ~~not~~ surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • 1year 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	**Appendix E: WOMEN OF CHILDBEARING POTENTIAL AND BIRTH CONTROL METHODS** Women of **non**-childbearing potential are defined as: • surgically(documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile • 1year 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	• Correction of wording regarding childbearing potential • 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 post-menopausal
APPENDIX H: PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS **Disallowed Concomitant Medications** 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.	**APPENDIX H: PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS** **Disallowed Concomitant Medications** Systemic steroids are not allowed during the double-blind treatment period of this long-term extension study. Note that **intranasal**, intra-articular steroid injections, steroid ear drops, steroids for ocular use, and steroid creams for topical use are permitted during the study.	• 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.
APPENDIX G: HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL	**APPENDIX G: HANDLING, LABELING, STORAGE, AND ACCOUNTABILITY FOR INVESTIGATIONAL MEDICINAL**	• Updating equilibration time to syringes prior administration into IV bag (45-60 minutes)

PRODUCT(S) 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. Preparation instructions for sc injections: IMP should be allowed to equilibrate at room temperature for ~~15 to 30~~ 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.	**PRODUCT(S)** Preparation instructions for iv infusions: **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.	• 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.

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] or [redacted] if you have any questions or concerns regarding this letter.

Sincerely,

[redacted]

Signature

Name: [redacted]

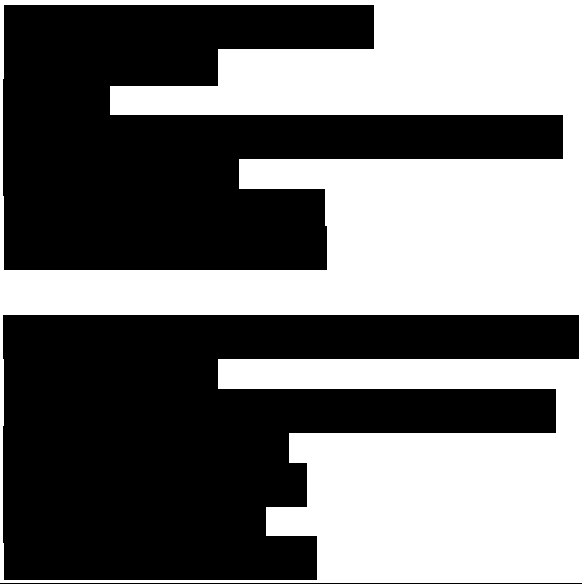
Title [redacted]

Department Clinical Development, Teva Pharmaceuticals

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	[redacted]
Legal Representative of the Sponsor in the European Union	[redacted]
Sponsor's Medical Expert/Contact Point designated by the Sponsor for Further Information on the Study	[redacted]

Sponsor's Contact Point designated by the sponsor for further information on the study	[redacted]
Study Principal Investigator	[redacted]

Sponsor's Representative of Global Patient Safety and Pharmacovigilance For **serious adverse events:** Send by email to the local safety officer/contract research organization. The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel identified above for further instruction.	
Contract Research Organization	PRA 4130 Park Lake Avenue Suite 400 Raleigh, NC 27612 NCGS, Inc. 288 Meeting Street Suite 400 Charleston, SC 29401
Central Clinical Laboratory	Q^2 Solutions Central Laboratory
Central Electrocardiogram Evaluation	eResearch Technology, Inc. 1818 Market Street Philadelphia, PA 19103
Bioanalytical Pharmacokinetics Evaluation	

Bioanalytical Immunogenicity Evaluation	[redacted]
Pharmacogenomics/Biomarker Evaluation	[redacted]
Electronic Clinical Outcome Assessment	eResearch Technology, Inc. 1818 Market Street Philadelphia, PA 19103
Web and Phone Integrated Interactive Response Technology	Y-PRIME

APPENDIX B. STUDY PROCEDURES AND ASSESSMENTS BY VISIT

Patients Enrolling in the Study from the Pivotal Studies

1. **Procedures Before Investigational Medicinal Product (IMP) Treatment (Visit 1)**

Visit 1 of the current study corresponds with the end-of-treatment (EOT) visit (visit 5) of the pivotal efficacy studies. EOT visit procedures/assessments must be completed before the patient begins participation in this study, and the EOT procedures/assessments will not be repeated at visit 1 of this study. The EOT visit procedures/assessments are detailed in the protocols for Studies TV48125-CNS-30056 and TV48125-CNS-30057. The following procedures will be performed before receiving investigational medicinal produce (IMP) at visit 1:

- Obtain written informed consent before any other study-related procedures are performed. In addition to the patient, the partner or family member who will complete the Impact on Partner and Family questionnaire, if applicable, will also provide written informed consent.
- Patients participating in the wearable sensor substudy will be asked to provide consent to continue participating in the substudy during this long-term safety study.
- Perform urine beta-human chorionic gonadotropin (β-HCG) test (women of childbearing potential [WOCBP] only).
- Review inclusion and exclusion criteria.

Patients enrolled in the wearable sensor substudy will continue to wear the digital wearable device on the wrist throughout the double-blind treatment period of this study provided they consent to continued participation in the substudy.

2. **Treatment Period (Visits 1 Through 11 [Weeks 0 Through 40 ± 3 Days])**

Patients will complete entries of cluster headache (CH) attack information (ie, occurrence and number of CH attack[s]) using electronic diary devices daily from visit 1 through visit 11 (week 40). Refer to Section 6.2 for additional details.

Procedures/assessments by visit during the double-blind treatment period are detailed in the following sections.

Visit 1 (Day 0 [Week 0])

After completing predose assessments (see Procedures Before IMP Treatment), patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+ 10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Week 1 (Day 7)

Patients will complete the Patient Global Impression of Change (PGIC) scale and the Patient-Perceived Satisfactory Improvement (PPSI) at 1 week after receiving IMP using the electronic diary device.

Visit 2 (Week 4 ± 3 Days)

The following predose procedures/assessments will be performed at visit 2:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform full physical examination, including weight measurement.
- Inquire about adverse events.
- Inquire about concomitant medications.
- Perform urine β-HCG test (WOCBP only).
- Complete the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) Since Last Visit version.
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Administer 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).
- Complete the PPSI.
- Complete the PGIC scale.
- 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 or to return to the investigational center within ±3 days of the patient's visit if unable to appear at the same time.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 (±15 minutes) hour 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 investigational center.

Visit 3 (Week 8 ± 3 Days)

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

- 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 urine β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Complete the eC-SSRS Since Last Visit version.
- Complete the PPSI.
- Complete the PGIC scale.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 4 (Week 12 ± 3 Days)

The following predose procedures/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).
- Perform triplicate 12-lead electrocardiograms (ECGs).
- 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 β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Obtain a 5-mL blood sample for serum antidrug antibody (ADA) analysis.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain a 17-mL blood sample for biomarker analysis (8.5 mL for serum, 6 mL for plasma, and 2.5 mL for RNA).
- Complete the eC-SSRS Since Last Visit version.
- Administer the HADS, EQ-5D questionnaire, SF-12 questionnaire, and WPAI questionnaire.
- Complete the PPSI.
- Complete the PGIC scale.
- 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 or to return to the investigational center within ±3 days of the patient's visit if unable to appear at the same time.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 5 (Week 16 ± 3 Days)

The following procedures/assessments will be performed at visit 5:

- Review electronic diary data.
- Review study compliance.
- 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 urine β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 6 (Week 20 ± 3 Days)

The following predose procedures/assessments will be performed at visit 6:

- 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 urine β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 7 (Week 24 ± 3 Days)

The following predose procedures/assessments will be performed at visit 7:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform triplicate 12-lead ECGs.
- 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 β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.

- Obtain a 5-mL blood sample for serum ADA analysis.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain a 17-mL blood sample (8.5 mL for serum, 6 mL for plasma, and 2.5 mL for RNA) for biomarker analysis.
- Complete the eC-SSRS Since Last Visit version.
- Administer the HADS, EQ-5D questionnaire, SF-12 questionnaire, and WPAI questionnaire.
- Complete the PPSI.
- Complete the PGIC scale.
- 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 or to return to the investigational center within ±3 days of the patient's visit if unable to appear at the same time.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 8 (Week 28 ± 3 Days)

The following predose procedures/assessments will be performed at visit 8:

- Review electronic diary data.
- Review study compliance.
- 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 urine β-HCG test (WOCBP only).

- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 9 (Week 32 ± 3 Days)

The following predose procedures/assessments will be performed at visit 9:

- 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 urine β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Complete the eC-SSRS Since Last Visit version.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Visit 10 (Week 36 ± 3 Days)

The following predose procedures/assessments will be performed at visit 10:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform triplicate 12-lead ECGs.
- 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 β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Obtain a 5-mL blood sample for ADA analysis.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain a 17-mL blood sample for biomarker analysis (8.5 mL for serum, 6 mL for plasma, and 2.5 mL for RNA).
- Complete the eC-SSRS Since Last Visit version.
- Administer the HADS, EQ-5D questionnaire, SF-12 questionnaire, and WPAI questionnaire.
- Complete the PPSI.
- Complete the PGIC scale.
- 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 or to return to the investigational center within ±3 days of the patient's visit if unable to appear at the same time.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.

After completing predose assessments, patients who are not in CH remission will be treated with IMP. Refer to Section 5.1.1.1 for details.

The following procedures/assessments will be performed after dosing:

- Perform local injection site assessment immediately (+10 minutes) and at 1 hour (±15 minutes) 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 investigational center.

Additional Visit(s) for Patients in the Wearable Sensor Substudy

[redacted]

End-of-Treatment Visit (Visit 11 [Week 40 ± 3 Days])/Early Withdrawal Visit

The following procedures/assessments will be performed at the EOT/early withdrawal visit:

- Review electronic diary data.
- Review study compliance.
- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform triplicate 12-lead ECGs.
- 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 β-HCG test (WOCBP only).
- Obtain a 4-mL blood sample for pharmacokinetics analysis.
- Obtain a 5-mL blood sample for ADA analysis.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain a 17-mL blood sample (8.5 mL for serum, 6 mL for plasma, and 2.5 mL for RNA) for biomarker analysis.

- Complete the eC-SSRS Since Last Visit version.
- Administer the HADS, EQ-5D questionnaire, SF-12 questionnaire, and WPAI questionnaire.
- Complete the PPSI and the PGIC scale.
- Collect the electronic diary device.
- 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 or to return to the investigational center within ±3 days of the patient's visit if unable to appear at the same time.
- Perform wearable sensor device check and compliance check for patients enrolled in the wearable sensor substudy.
- Collect wearable sensor device from patients enrolled in the wearable sensor substudy.

3. **Procedures after IMP Treatment**

Follow-up Visit (Visit 12 [Week 68 ± 1 Week])

Patients who participate in the study in compliance with the protocol for the entire treatment period (ie, from visit 1 through visit 11) will be considered to have completed the study. Patients may be treated with standard of care following completion of visit 11. See Section 3.1 for the definition of the end of study.

Patients who complete the double-blind treatment period will have a follow-up visit approximately 7.5 months (5 half-lives) after the final dose of IMP. The following procedures/assessments will be performed at this visit:

- Perform vital signs measurements (includes systolic and diastolic blood pressure, pulse, and body temperature).
- Perform physical examination (including weight).
- Inquire about adverse events.
- Inquire about concomitant medications.
- Complete the eC-SSRS Since Last Visit version.
- Obtain a 5-mL blood sample for ADA analysis.
- Obtain a 5-mL urine sample for biomarker analysis.
- Obtain a 17-mL blood sample (8.5 mL for serum, 6 mL for plasma, and 2.5 mL for RNA) for biomarker analysis.

Patients who discontinue treatment prematurely must be encouraged to continue to attend the regular scheduled visits, and complete the prescribed safety and efficacy evaluations through the EOT visit (visit 11 [week 36]) and the follow-up visit (visit 12 [week 40]), if at all possible.

Patients who both discontinue treatment and also withdraw from the study should have EOT (early withdrawal) visit procedures/assessments (see Table 4) performed on the last day the patient receives the IMP, or as soon as possible thereafter. The patient should also return for the follow-up visit approximately 7.5 months after the last dose of IMP if at all possible.

Procedures for patients who withdraw prematurely from the study are described in Section 4.3. Patients should be treated with standard of care after termination of the study as appropriate.

Patients with ongoing adverse events or clinically significant abnormal laboratory test results (as interpreted by the investigator) will be monitored as described in Section 7.1.2.

4. **Unscheduled Visits**

An unscheduled visit may be performed at any time during the study, at the patient's request or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be recorded on the case report form as well as any other data obtained (eg, adverse events, concomitant medications and treatments, and results from procedures or tests).

Procedures performed during unscheduled visits include the following:

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

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

Patients Enrolling in This Study for Evaluation of Antidrug Antibodies and Safety (Adverse Events and Concomitant Medications)

1. **Visit 1**

The following procedures/assessments will be performed at visit 1 for patients who enroll in this study for the purpose of evaluating ADAs, and safety (adverse events and concomitant medications):

- Obtain written informed consent before any other study-related procedures are performed.
- Inquire about adverse events.
- Inquire about concomitant medications.

2. **Follow-up Visit (Visit 12 – Approximately 7.5 months after the last dose of IMP during the pivotal efficacy study)**

Patients enrolling in this study for the purpose of evaluating ADAs and safety (adverse events and concomitant medications) only will attend a visit approximately 7.5 months after receiving the last dose of IMP (during the pivotal efficacy studies). The following procedures/assessments will be performed at this visit:

- Inquire about adverse events.
- Inquire about concomitant medications.
- Obtain a 5-mL blood sample for ADA analysis.

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 Independent Ethics Committee/Institutional Review Board (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 Good Clinical Practice (GCP) guidelines; noncompliance to investigational medicinal product administration; and use of prohibited medications. All 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 Good Clinical Practice (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 enrolled 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 standard operating procedures (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 monitor(s) 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 (case report forms [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 Independent Ethics Committee/Institutional Review Board (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 (ICF), 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 ICFs, and copies will be given to the patient. It will also be explained to the patient that a 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 the 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 confidential at all times. In case report forms (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, 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 products (IMPs) 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, cytochrome P450 [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 immunoglobulin G2 isotype, which 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 proinflammatory cytokine release in human whole blood (Study 111320). Fremanezumab did not elicit significant cytokine release (TNF α, IL-6, INF γ, or IL-1β) in any donor including at concentrations up to 100 μg/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. Such methods include:

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

- Intrauterine device and intrauterine hormone-releasing system 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; and cap, diaphragm, or sponge with spermicide. The combination of male condom with either 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, postovulation 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 patients 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, 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 and placebo will be provided in prefilled syringes contained in uniquely numbered kits and stored (refrigerated at 2°C to 8°C) at the investigational center. At the time of each study visit, the interactive response technology will be queried, and site personnel will retrieve the appropriately numbered kit(s). Kit numbers will be entered into the case report form.

Preparation instructions for subcutaneous (sc) injections: [redacted] A 1.5 mL volume from each syringe in each visit's 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) and protected from light; the investigational center should have a process for monitoring the IMP storage temperature.

Diversion is considered to have occurred when the legal supply chain of prescription 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 Code of Federal Regulations 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 center should provide a certificate of destruction. If the investigational center 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 the IMP will be returned to the sponsor or designee.

APPENDIX H. PREVENTIVE CLUSTER HEADACHE MEDICATIONS AND DISALLOWED MEDICATIONS

Disallowed Medications Commonly Prescribed for Cluster Headache

The following medications will be considered as being used for the prevention of cluster headache attacks regardless of the initial indication:

- verapamil
- lithium
- methysergide
- valproate
- topiramate

Patients must start tapering these preventive medications as soon as they begin this study. The period of time needed to taper off these medications will be based on the investigator's medical judgment but should not exceed 1 month from the beginning of participation in this study.

Disallowed Concomitant Medications

Systemic steroids are not allowed during the double-blind treatment period of this long-term extension study.

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

APPENDIX I. ICHD-3 BETA DIAGNOSTIC CRITERIA

Refer to the International Classification of Headache Disorders, third edition (ICHD-3 beta) Diagnostic Criteria (Headache Classification Committee of the International Headache Society 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) [1]

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 ≥1 month

3.1.2 Chronic cluster headache

Diagnostic criteria:

A) Attacks fulfilling criteria for 3.1 Cluster headache and criterion B

[1] 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

B) Occurring without a remission period or with remissions lasting <1 month, for ≥1 year

APPENDIX J. GUIDANCE ON SAFETY MONITORING

Guidance on Monitoring Patients with Elevated Liver Function Tests

Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT], and alkaline phosphatase [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 ≥2 × the upper limit of the normal range (ULN) (including patients whose baseline ALT or AST levels are ≥2 × and ≤3 × 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.[2] 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 investigational 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 ≥3 × ULN

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

- The 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 international normalized ratio (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 ≥3 × the ULN

[2] 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.

- the baseline value was above the ULN and ALT or AST is ≥2 × the baseline value

Additional Tests/Evaluations:

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

- 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 ≥3 × (>3.5 × the ULN if the Baseline Value is >2.5 × the ULN) but <5 × the ULN

In addition to the above procedures required for any elevation to levels >3 × 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 (±2 days), 8 (±2 days), 14 (±3 days), and 28 (±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 (≥3 × the ULN in case baseline was within the normal range or ≥2 × the ULN in case the baseline value was above ULN but still <5 × 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 ≥5 × but <8 × the ULN

In addition to the above procedures required for any elevation to levels >3 × 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 ≥8 × the ULN

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

- The IMP should be discontinued immediately, and the early withdrawal visit should be performed.
- For follow-up guidance, please see 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 ≥3 × the ULN, combined with INR >1.5 × the ULN or total bilirubin >2 × the ULN
- any increase in ALT or AST to ≥3 × the ULN, which is accompanied by symptoms clearly associated with impaired liver function (eg, vomiting, nausea, fever, rash, 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 ≥5 but <8 × the ULN, which is persistent for ≥2 weeks of repeated measurements
- any increase in ALT or AST to levels ≥8 × the ULN
- in any case where monitoring of liver enzymes cannot be performed according to the protocol guidance

Follow-Up of Liver Enzymes after Stopping Rules Are Met

- A patient who meets the above criteria for discontinuation of the IMP should be invited to the investigational center 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], and hypoxemia)
    b. reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, and 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, and swollen lips-tongue-uvula)
    b. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, and hypoxemia)
    c. reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, and 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 center should have a resuscitation cart nearby.

APPENDIX L. TOTAL BLOOD VOLUME

Total blood volume to be collected for each patient in this study is approximately 205.5 mL for scheduled tests. An additional 30 mL of blood may be collected in the event of follow-up for liver enzymes as detailed in Appendix J.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Serum chemistry	3.5	4	14
Serum pregnancy	3.5	1	3.5
Hematology	2	4	8
Coagulation	4.5	4	18
Pharmacokinetics	4	13[a]	52
ADA[b]	5	5	25
Biomarker Serum	8.5	5	42.5
Biomarker Plasma	6	5	30
Biomarker RNA	2.5	5	12.5
Total	**--**	**22**	**205.5**

[redacted]

[b] 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).

ADA=antidrug antibody; ECG=electrocardiogram; IMP=investigational medicinal product.

The total blood volume to be collected for each patient enrolling in this for evaluation of ADAs (one 5-mL blood sample) and safety (adverse events and concomitant medications) is approximately 5 mL.

APPENDIX M. CLINICAL LABORATORY TESTS

Clinical Laboratory Tests

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

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, 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

Serum or 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 –70ºC 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 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, for approximately 10 minutes, at 2 C 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, polypropylene tubes (Sets A and B).

Label of samples should include study number, patient randomization number, nominal collection time, Set A or B, and indication that they are antidrug antibody (ADA) samples. Serum samples will be stored at a temperature of -70 ºC to -20°C 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 –70ºC 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 intact.

APPENDIX P. EXPLORATORY BIOMARKERS SAMPLES

[redacted]

Shipment and Analysis of Samples

[redacted]

APPENDIX Q. PHARMACOGENOMIC ASSESSMENTS

Pharmacogenomic assessment will be performed based on study results. Samples collected during the pivotal efficacy studies 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 investigational medicinal product (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 7.1.5.3, 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 the equivalent, before they are transcribed to the case report form (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, Independent Ethics Committee/Institutional Review Board (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, and 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 clinical data management system (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, and site 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 standard operating procedures (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, and electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the investigational medicinal products
- 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 contract research organization 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). 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

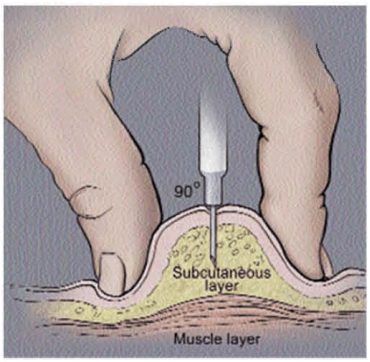
The publications committee established by the sponsor will oversee this process. Additional publications may follow. Policies regarding the publication of the study results are defined in the financial agreement.

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 subcutaenous 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 sucutaneous 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

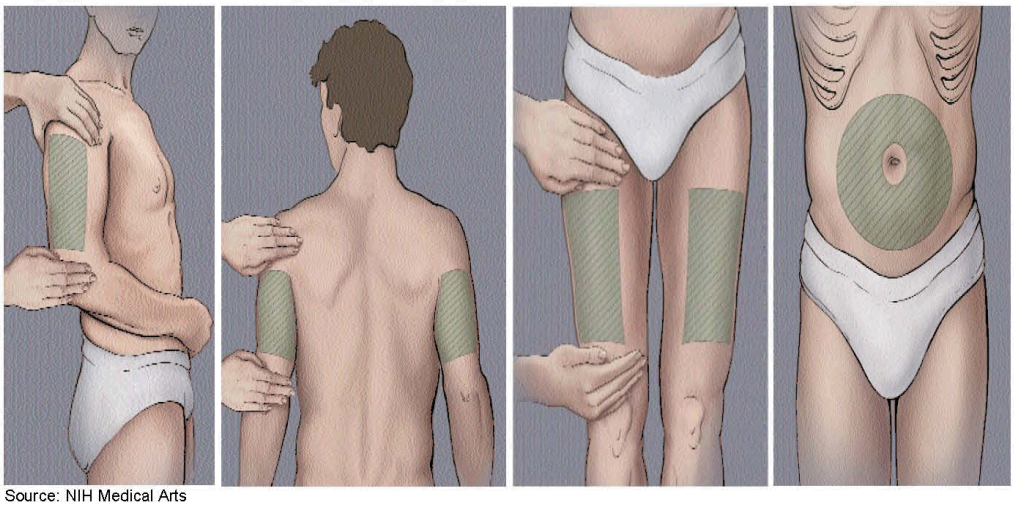
Drawing up medication

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 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

National Institutes of Health Clinical Center
Bethesda, MD 20892
Questions about the NIH Clinical Center?
http://www.cc.nih.gov/comments.shtml
09/2015