Clinical Study Protocol

A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-Label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

Study Number TV48125-CNS-20024

NCT03347188

Protocol with Amendment 02 Approval Date: 30 March 2020

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Short Study Title:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study, Including an Open-Label Period, to Evaluate the Efficacy and Safety of Fremanezumab in the Treatment of Posttraumatic Headache (PTH)

Lay Language Title:
A Study to Test if Fremanezumab Reduces Headache in Patients with Posttraumatic Headache

Efficacy and Safety Study (Phase 2)

IND number: 106533; BLA number: Not Applicable; EudraCT number: Not Applicable

EMA Decision number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

Protocol Approval Date: 27 June 2017

Protocol with Amendment 01 Approval Date: 25 March 2019

Protocol with Amendment 02 Approval Date: 30 March 2020

Sponsor

Teva Branded Pharmaceutical
Products R&D, Inc.
145 Brandywine Parkway
West Chester, Pennsylvania 19380
United States of America

Information regarding clinical laboratories and other departments and institutions is found in Appendix A

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).

Confidentiality Statement

AMENDMENT HISTORY

The protocol for Study TV48125-CNS-20024 (original protocol dated 27 June 2017) has been amended and reissued as follows:

Amendment 02	30 March 2020 87 patients have been randomized/enrolled to date.
Letter of Clarification 09	30 October 2019
Letter of Clarification 08	24 September 2019
Letter of Clarification 07	01 August 2019
Letter of Clarification 06	18 April 2019
Amendment 01	25 March 2019 70 patients have been randomized/enrolled to date.
Letter of Clarification 05	01 October 2018
Letter of Clarification 04	06 February 2018
Letter of Clarification 03	11 December 2017
Letter of Clarification 02	16 November 2017
Letter of Clarification 01	10 November 2017

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

INVESTIGATOR AGREEMENT

Original Protocol Dated 27 June 2017

Clinical Study Protocol with Amendment 02

IND number: 106533; BLA number: Not Applicable; EudraCT number: Not Applicable; EMA Decision number of Pediatric Investigation Plan: Not Applicable; Article 45 or 46 of 1901/2006 does not apply

A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-Label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

Principal Investigator: [redacted]

Title: [redacted]

Address of Investigational Center: [redacted]

Tel: [redacted]

I have read the protocol with Amendment 02 and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience, and training to conduct this clinical research study. The signature below constitutes 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**
[redacted]		

SPONSOR PROTOCOL APPROVAL

Sponsor's Authorized Representative	Signature	Date
[redacted]	[redacted]	30 MAR 2020

COORDINATING INVESTIGATOR AGREEMENT

Original Protocol Dated 27 June 2017

Clinical Study Protocol with Amendment 02

IND number: 106533; BLA number: Not Applicable; EudraCT number: Not Applicable

EMA Decision number of Pediatric Investigation Plan: Not Applicable

Article 45 or 46 of 1901/2006 does not apply

A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-Label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

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Coordinating Investigator [redacted]

Title: Director

Address of Investigational Center: [redacted]

Tel: [redacted]

Coordinating Investigator [redacted]	**Signature**	**Date**

CLINICAL STUDY PROTOCOL SYNOPSIS

with Amendment 02

Study TV48125-CNS-20024

Title of Study: A Phase 2, Multicenter, Randomized, Proof-of-Concept, Double-Blind, Placebo-Controlled, Parallel-Group Study, Including an Open-label Period, Evaluating the Efficacy and Safety of 1 Subcutaneous Dose Regimen of Fremanezumab for the Treatment of Posttraumatic Headache (PTH)

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc., 145 Brandywine Parkway, West Chester, Pennsylvania 19380, USA

Investigational New Drug (IND) Number: 106533

Biological License Application (BLA) Number: Not applicable

EudraCT Number: Not applicable

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); a humanized anti-calcitonin gene-related peptide (CGRP) monoclonal antibody

EudraVigilance (EV) code for the IMP: Not applicable

Type of the Study: Efficacy and safety study (Phase 2)

Indication: Fremanezumab is planned as an indication for the treatment of posttraumatic headache (PTH).

Is this study conducted to investigate the New Use of an approved, marketed product? Yes

Number of Investigational Centers Planned: This study is planned to be conducted in approximately 32 investigational centers.

Countries Planned: The study is planned to be conducted in the United States.

Planned Study Period: The study is expected to be executed between the period of Q4 2017 and Q2 2020.

Number of Patients Planned (total): The total number of patients planned was approximately 172 (86 patients per treatment group). Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.

Study Population: The study population will be composed of male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by International Classification of Headache Disorders 3rd revision [ICHD-3] (beta version) criteria).

This will include patients with headache attributed to mild, traumatic injury of the head and patients with headache attributed to whiplash.

Primary and Secondary Objectives and Endpoints

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

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fremanezumab administered subcutaneously (sc) in adult patients with posttraumatic headache (PTH).	The primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.
A **secondary objective** is to evaluate the efficacy of fremanezumab administered sc in adult patients with PTH.	The **secondary efficacy endpoints** are: • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period of treatment with the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate

Objectives	Endpoints
	severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (visit 2) in disability score, as measured by the 6-item Headache Impact Test (HIT-6) at week 12 after the first dose of the IMP • mean change from baseline (visit 2) in the assessment of patient satisfaction, as measured by the Patient Global Impression of Change scale, at 4, 8, and 12 weeks after the first dose of the IMP
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered sc in adult patients with PTH compared with placebo and during the open-label period.	The **safety and tolerability endpoints** are: • occurrence of adverse events during the study • clinically significant changes in physical examinations, including body weight • clinical laboratory (serum chemistry, hematology and coagulation, and urinalysis) test results at each visit • vital signs (blood pressure, respiratory rate, body temperature, and pulse) measurements at each visit Note: Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity. • 12-lead electrocardiogram (ECG) findings at each visit • use of concomitant medication during the study • number (%) of patients who did not complete the study (day 168, end-of-study) • number (%) of patients who did not complete the study due to adverse events • local tolerability at the injection site (ie, erythema, induration, ecchymosis, and pain) at the following time points postdose: day 0, day 28, and day 56 • hypersensitivity reaction assessment • Columbia Suicide Severity Rating Scale (C-SSRS)

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

ADA=antidrug antibody; C-SSRS=Columbia Suicide Severity Rating Scale, ECG=electrocardiogram; HIT-6=6-item Headache Impact Test; IMP=investigational medicinal product; PTH= posttraumatic headache; sc=subcutaneous.

[redacted]

General Study Design: This is a multicenter, randomized, proof-of-concept, double-blind, placebo-controlled, parallel-group study, including an open-label period, evaluating the efficacy and safety of 1 subcutaneous dose regimen of fremanezumab in adult patients with PTH. The study will consist of a screening visit, a baseline period, a double-blind treatment period lasting approximately 12 weeks, and an open-label period lasting approximately 12 weeks.

The total duration of patient participation in the study is planned to be approximately 28 weeks, including a baseline period lasting approximately 4 weeks, a double-blind treatment period lasting 12 weeks, and an open-label period lasting 12 weeks.

Patients will complete a screening visit (visit 1) after providing informed consent, and eligible patients will enter a baseline period lasting approximately 4 weeks (28+3 days), during which they will enter their baseline PTH information into a daily electronic headache diary. Patients meeting eligibility requirements will be randomly assigned to 1 of 2 treatment groups with fremanezumab or placebo in a 1:1 ratio. Treatment assignment will take place with stratification based on the duration of the patient's history of PTH (<12 months and ≥12 months duration).

Screening results will be reviewed for eligibility, additional baseline assessments will be administered, and the first treatment administration will occur at visit 2. Patients will return to the study center approximately every 4 weeks (visit 3 and visit 4) for a continuation of the blinded treatment administered sc; for safety and efficacy assessments; and for blood and urine sampling for pharmacokinetics, immunogenicity, and biomarker analysis. At visit 5, all patients will proceed directly to an open-label treatment phase, with fremanezumab administered sc. Patients will then return to the study center approximately every 4 weeks (visits 6 and 7) for continued open-label treatment and safety tolerability and efficacy assessments. Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP.

A database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.

Patients who complete all scheduled visits will have procedures and assessments performed at visit 8. Patients who withdraw from the study before completing either the double blind or the open label treatment phases will have visit 8 procedures and assessments performed at their final visit. For all patients in the study, the end-of -treatment visit (visit 8) is defined as the final visit of the study and the conclusion of all study activities for the patient; patients will not receive any further treatments with IMP and will be treated according to guidelines and treating physicians' discretion.

However, a final database lock will occur following the end-of-treatment visit (visit 8) of the last patient for analysis of the study data.

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

This is a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, including an open-label period, to evaluate the safety and efficacy of 1 subcutaneous dose regimen of fremanezumab in adult patients aged 18 to 70 years, inclusive, for the prevention of PTH. Patients who provide written informed consent and complete a screening visit will enter a baseline period lasting approximately 4 weeks (28+3 days), during which they will record their PTH symptoms into a daily electronic diary application, to establish a clinical baseline. Patients will return to the study center after completing the baseline period, and those who meet all eligibility requirements will be randomized to receive the test IMP or placebo IMP. Patients will then return to the study center monthly for continued treatment with 2 further doses of sc fremanezumab or placebo (a total of 12 weeks placebo-controlled treatment phase), followed by a 12-week open-label treatment phase in which all patients will receive 3 monthly doses of sc fremanezumab. A final visit will occur approximately 28 days after the last dose of IMP, which should occur at approximately 24 weeks after the first dose of IMP, to evaluate treatment efficacy, ADAs, fremanezumab concentrations and safety.

Efficacy will be evaluated using PTH data entered daily into an electronic diary throughout the 12-week placebo-controlled treatment period and administration of questionnaires to evaluate PTH-related disability, change in quality of life, health status, and satisfaction with treatment. The safety will be evaluated through adverse event and concomitant medication inquiries, ECGs, vital signs measurements, clinical laboratory tests, physical examinations, injection site reaction and pain assessments, assessments for anaphylaxis and severe hypersensitivity, and administration of the Patient Health Questionnaire (PHQ)-2/PHQ-9 and C-SSRS. In addition, blood will be collected for pharmacokinetics, immunogenicity, biomarker analyses, and urine will be collected for biomarker analysis.

Method of Randomization and Blinding: Randomization will be performed using electronic interactive response technology (IRT). Blinded treatment will be administered subcutaneously at visit 2, visit 3, and visit 4 for a total of 3 doses.

The sponsor, investigators, study staff (except for staff involved in bioanalytical analyses), and patients will be blinded to treatment assignment. A computer-generated master randomization list will be provided to drug packaging facilities. Packaging vendor(s) will package active and placebo IMP into single-visit kits according to Good Manufacturing Practice procedures. Kits will be identical in appearance and will contain prefilled syringes (active or placebo). Adequate kit supply for upcoming study visits will be managed by Medidata and kept refrigerated at 2°C to 8°C on site.

Patients meeting eligibility criteria in the screening procedure will be randomized if they meet the additional clinical eligibility criteria as recorded in their baseline headache diaries: (1) patients must record 8 or more headache days of moderate to severe intensity (defined as a day when a patient reports at least 4 hours of headache [not necessarily consecutive] of at least moderate severity at any time during the headache; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache [regardless of duration or severity]) during the baseline period, and (2) electronic diary compliance must be at least 75% during the baseline period for randomization eligibility and at least 75% during the double-blind treatment period, during which the patient cannot miss more than 7 days of recording nor more than 4 days in a row. Randomization will be performed using electronic IRT. Patients will be

randomly assigned with stratification based on the PTH onset (<12 months and ≥12 months since the brain injury) in a 1:1 ratio to receive fremanezumab or placebo, as assigned by the IRT. The IRT will centrally manage initial IMP supply, maintenance of adequate IMP supplies at the investigational centers, and study randomization.

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

Investigational medicinal products are defined as the test IMP and placebo IMP. The IMPs used in this study are described in the table below:

IMP name	Fremanezumab	Placebo IMP
Company-assigned number	Fremanezumab (formerly TEV-48125, LBR-101, PF-04427429, or RN307)	Not applicable
Product configuration	Prefilled syringes	Prefilled syringes
Unit dose strength(s)/Dosage level(s)	For sc administration: 2.25 mL prefilled syringes (1.5 mL deliverable volume each) at a nominal concentration of 150 mg/mL fremanezumab	For sc administration: 2.25 mL prefilled syringes (1.5 mL deliverable volume each) with the same vehicle and excipients as those for the active injections
Route of administration	sc injection Fremanezumab will be administered by qualified study personnel who will retrieve the appropriately numbered kit containing the prefilled syringes.	sc injection Placebo will be administered by qualified study personnel who will retrieve the appropriately numbered kit containing the prefilled syringes.
Dosing instructions	**Arm A:** The contents of three prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) injections sc at visit 2, visit 3, and visit 4	**Arm B:** The contents of three prefilled syringes, each containing 1.5 mL placebo injections sc at visit 2, visit 3, and visit 4
Packaging	Fremanezumab will be contained in uniquely numbered kits and stored refrigerated at 2°C to 8°C at the investigational center.	Placebo will be contained in uniquely numbered kits and stored refrigerated at 2°C to 8°C at the investigational center.
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380

IMP=investigational medicinal product; sc=subcutaneous

Patients will be randomized into one of the following treatment groups:

1. **Arm A**: Fremanezumab 675-mg sc treatment group

   Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).

2. **Arm B**: Placebo treatment group

Patients randomized to placebo will receive placebo administered as 3 sc injections (1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).

Test IMP: Fremanezumab

Placebo IMP: The placebo will consist of the same vehicle and excipients as those for fremanezumab.

Study Duration: The overall duration of the study will be approximately 2 years from Q4 2017 until approximately Q2 2020.

Open-Label Period: Patients will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20).

Duration of Patient Participation and Maximal Exposure to IMP: The total duration of patient participation in the study is planned to be approximately 28 weeks, including a baseline period lasting approximately 4 weeks, a double-blind treatment period lasting 12 weeks, and an open-label period lasting 12 weeks.

Patients are expected to complete the entire duration of the study.

End of Study: End-of-study (EOS) is defined as the last safety visit (visit 8).

Plans for Treatment or Care After the Patient Has Ended Participation in the Study: No treatment is planned by the sponsor after the EOS (visit 8). Patients will thereafter be treated with standard of care as judged to be appropriate by the patient's caregiver.

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

a. The patient is capable of giving signed informed consent as described in Appendix C of the protocol, which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol.

b. The patient is a man or woman 18 to 70 years of age, inclusive.

c. The patient has a body weight ≥45 kg.

d. Traumatic injury to the head has occurred, defined as a structural or functional injury resulting from the action of external forces. These include striking the head with or the head striking an object, penetration of the head by a foreign body, forces generated from blasts or explosions; or whiplash has occurred, defined as sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

e. The patient has a diagnosis of PTH as per the ICHD-3 (beta version) criteria:

   – Headache is reported to have developed within 7 days after one of the following:

      ○ mild traumatic injury to the head

      ○ regaining of consciousness following the injury to the head

      ○ discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head

In addition, the following criteria should be met:

- Headache persists for >1 month after injury to the head

f. During the baseline period, the patient has at least 8 headache days of at least moderate severity, defined as a day when a patient reports at least 4 hours of headache (not necessarily consecutive) and at its worst at any point has at least moderate severity; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity).

g. The patient demonstrated compliance with the electronic diary during the baseline period by entry of headache data at a minimum of 75% compliance.

h. The patient is not using preventive medications for headache (presented in Appendix F of the protocol) (ie, at least 5 half-lives have passed since last use) or is using them in a dose and regimen that have been stable for at least 2 months prior to beginning the baseline period.

i. Women may be included only if they have a negative serum beta-human chorionic gonadotropin test at screening and a negative urine pregnancy test at baseline, are sterile, or postmenopausal.

j. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 weeks after the last IMP administration.

k. Men must be sterile or, if they are potentially fertile or reproductively competent (ie, not surgically or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, a condom for the duration of the study and for 30 weeks after the last IMP administration. Definitions of WOCBP, sterile and postmenopausal women, male contraception, and highly effective birth control methods, including examples, are given in Appendix D of the 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 previous history of brain imaging showing evidence of intracerebral hemorrhage, subdural or epidural hematomas, or subarachnoid hemorrhage as a consequence of the traumatic head injury. Brain images with structurally insignificant changes, as discussed and approved by the sponsor, will be reviewed by the sponsor on a case-by-case basis.

b. The patient has PTH attributed to craniotomy.

c. The patient has whiplash and subsequent headache but no history of head injury or concussion.

d. The patient has an existing headache history prior to the head trauma, unless the patient reports a significant worsening of at least 50% in the frequency and/or severity of the headaches and, in the opinion of the investigator, the patient fulfills criteria for PTH.

e. The patient is using analgesic medications containing opioids (including codeine) or a barbiturate on average more than 15 days per month.

f. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days (or 90 days for biologics) or 5.5 half-lives, whichever is longer, of the IMP or is currently participating in another study of an IMP (or a medical device) prior to screening.

g. The patient has had exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, and fremanezumab) during the 6 months prior to the day of the screening visit.

h. The patient is currently being treated with onabotulinumtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the 3 months prior to the screening visit.

i. The patient has been implanted with any electronic devices for headache prevention during the 3 months prior to the screening visit or is currently using any implanted or externally applied stimulator or device.

j. The patient has been treated with a nerve block for head and/or neck pain during the 3 months prior to the screening visit.

k. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol.

l. The patient has a history or presence of other medical illness that, in the opinion of the investigator indicates a medical problem that would preclude study participation.

m. The patient is a pregnant or lactating woman or plans to become pregnant during the study.

n. The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease or has any clinically significant uncontrolled medical condition (treated or untreated) at the discretion of the investigator.

o. The patient has any psychiatric condition or evidence of significant active or unstable psychiatric disease that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

p. The patient has major depression as assessed by the 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9) at screening. Any patient with a score ≥15 should be considered to have major depression and should be referred for appropriate treatment. Patients with lower scores (5 to 14) may also have major depression, and they should be carefully evaluated by the investigator for the presence of additional symptoms.

q. The patient has a history of alcohol abuse or recreational drug abuse or at the discretion of the investigator is suspected of abusing alcohol or recreational drugs.

r. The patient has any lifetime history of suicidal behaviors (suicide attempts, interrupted attempts, aborted attempts, suicidal ideation, or preparations for suicide).

s. The patient fulfills any of the following criteria:
   - mentally or legally incapacitated or unable to give consent for any reason
   - in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution
   - in current litigation for any civil or criminal offense
   - in current, ongoing or future litigation for the life of the study, relating to headaches, trauma or injury to the brain
   - unable to be contacted in case of emergency

t. The patient has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

[redacted]

Analysis of Primary Endpoint: The primary efficacy endpoint for this study will be derived from PTH data (ie, presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.

Analysis of Secondary Endpoints: Secondary efficacy endpoints will be derived from PTH data (ie, presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application. In addition, disability score will be derived from the HIT-6 assessment at time points detailed in Table 1 of the protocol.

Primary Efficacy Analysis: The primary efficacy endpoint, the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP, will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariates. A 95% confidence interval will be constructed for the least squares mean difference between the fremanezumab group and the placebo group, and the p-value will be presented.

The primary estimand for this study is defined by the following attributes:

- The target population includes male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by the ICHD-3 [beta version] criteria).
- The primary outcome measure is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP.
- The full analysis set (FAS) will be used for efficacy analyses. FAS is a subset of the ITT analysis set and includes only patients who receive at least 1 dose of IMP and have at least 1 postbaseline efficacy assessment on the primary endpoint. In the FAS, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.
- Treatment effect will be measured via ANCOVA method, including treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariates.

For patients assigned to active treatment who discontinue the study due to lack of efficacy, death, or adverse event, the proportion of headache days in the remainder of the analysis window will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to placebo. All other missing data for patients in either treatment group will be handled as follows:

- For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number of headache days will be calculated based on data available in that analysis window and prorated to 28 days.
- For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data. Sensitivity analyses will be conducted as defined in the statistical analysis plan.

Sensitivity Analysis: Sensitivity analysis will be conducted to explore the impact of missing data in the primary efficacy analysis. In particular, endpoints analyzed using an ANCOVA method will be analyzed using a mixed model for repeated measures method. The details will be described in the statistical analysis plan.

Secondary Efficacy Analysis: The continuous secondary efficacy endpoints will be analyzed using an analysis of variance method or a mixed-model for repeated measures. For the proportion of responders defined as 50% or more reduction from baseline in the monthly average headache days, the Cochran-Mantel-Haenszel test will be used stratified by PTH onset (<12 months and ≥12 months). For the key secondary endpoints, a 95% confidence interval will be constructed to compare the treatment effect between the fremanezumab group and the placebo group, and the p-value will be presented.

[redacted]

Multiple Comparisons and Multiplicity: Testing of statistical significance at a 2-sided alpha of 0.05 will be performed for the primary endpoint. If the primary endpoint meets statistical significance, then each of the key secondary endpoints will be tested for significance in a

pre-specified order at a 2-sided alpha of 0.05. If and when any p>0.05, no further comparisons will be interpreted inferentially. Details will be presented in the statistical analysis plan.

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 of the protocol) (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.

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

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 test IMP.

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 be provided as well.

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 case study report.

Tolerability Analysis: Injection site reaction assessment will be listed and summarized descriptively.

Pharmacokinetic Analysis: Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point. At the open-label period, pharmacokinetic plasma concentration results (fremanezumab) will be tabulated descriptively at each planned sampling time point by treatment group.
In addition, the most appropriate population pharmacokinetic model may be developed, and covariates that may affect it will be tested for inclusion in the model. If performed, this analysis will be reported separately.

Pharmacokinetic/Pharmacodynamic Analysis: The pharmacokinetics/pharmacodynamics relationship may be estimated by compartmental techniques. The pharmacokinetic parameters will be based on fremanezumab measurements. The pharmacodynamic endpoints will be the efficacy/safety response(s).

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

[redacted]

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, fremanezumab efficacy, and clinical safety will be evaluated. This analysis will be reported separately.

Planned Interim Analysis: There will be no formal interim analysis.

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	anti-drug antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
β-HCG	beta-human chorionic gonadotropin
BLA	biological license application
CDMS	clinical data management system
CFR	Code of Federal Regulations (USA)
CGRP	calcitonin gene-related peptide
CL/F	apparent total body clearance
C_{max}	maximum observed plasma drug concentration
CRF	case report form (refers to any media used to collect study data [ie, paper or electronic])
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GGT	gamma-glutamyl transpeptidase
GLP	Good Laboratory Practice
GPSP	Global Patient Safety and Pharmacovigilance
HIT-6	6-item Headache Impact Test
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders 3rd revision
IEC	Independent Ethics Committee

Abbreviation	Term
IgG2	immunoglobulin G2
IHS	International Headache Society
IMP	investigational medicinal product
IND	investigational new drug
IL	interleukin
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
iv	intravenous
LSO	local safety officer
PGIC	Patient Global Impression of Change
PHQ-2	2-item Patient Health Questionnaire
PHQ-9	9-item Patient Health Questionnaire
PK	pharmacokinetic(s)
PP	per-protocol
PTH	posttraumatic headache
RSI	reference safety information
sc	subcutaneous
SCAT-3	Sport Concussion Assessment Tool 3rd edition
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}	median time of maximum observed concentration
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state
V_z/F	apparent volume of distribution during the terminal phase
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Introduction

When a headache occurs for the first time in close temporal relation to trauma or injury to the head, it is coded as a secondary headache attributed to the trauma or injury. Headache attributed to trauma or injuries, or posttraumatic headache (PTH), accounts for approximately 4% of all symptomatic headaches (D'Onofrio 2014) and is among the most common secondary headache disorders. A large number of patients with headaches are at risk to have PTH, thus, PTH should be considered an important public health issue.

There are no specific headache features known to distinguish the subtypes of PTH from other headache types. They can resemble a range of primary headache conditions such as migraine (ie, moderate to severe intensity, pulsating, associated nausea or vomiting, light or sound sensitivity, and worsened with activity) or tension-type headache (ie, mild to moderate intensity, non-pulsating, light or sound sensitivity, but no nausea or vomiting), or one of a number of more uncommon headache syndromes (Finkel et al 2017). Rather, the diagnosis of PTH is largely dependent on the close temporal relationship between the trauma or injury and headache onset. PTH requires that the headache must be reported to have developed within 7 days of trauma or injury, or within 7 days of having regained consciousness, and/or ability to report pain when these have been lost following trauma or injury (IHS 2013).

The PTH may occur as an isolated symptom following trauma or injury or as one of a constellation of symptoms, commonly including dizziness, fatigue, reduced ability to concentrate, psychomotor slowing, mild memory problems, insomnia, anxiety, personality changes, and irritability. When several of these symptoms follow head injury, the patient may be considered to have a post-concussion syndrome. Posttraumatic sleep disturbances, mood disturbances, and psychosocial stressors can plausibly influence the development and perpetuation of headache.

The pathogenesis of PTH is most commonly in the absence of overt brain injury. Numerous factors that may contribute to its development include, but are not limited to, axonal injury, alterations in cerebral metabolism and cerebral hemodynamics, underlying genetic predisposition, psychopathology, and a patient's expectation of developing a headache after head injury (IHS 2013). It is recommended that treatment for secondary headache types, such as PTH, be consistent with the treatment of the primary headache type it most resembles (Lucas 2015).

Fremanezumab (formerly TEV-48125, LBR-101, PF-04427429, and RN307) is a fully humanized IgG 2a/kappa monoclonal antibody, which is being developed for administration by the subcutaneous (sc) route for the preventive treatment of migraine. Fremanezumab is a potent, selective calcitonin gene-related peptide (CGRP) binder that blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. Fremanezumab has been shown to be safe and efficacious 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).

The purpose of the study is to evaluate the efficacy and safety of fremanezumab administered subcutaneously for the prevention of PTH in adult patients.

1.2. Findings from Nonclinical and Clinical Studies

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

1.2.1. Nonclinical Studies

Fremanezumab was evaluated in nonclinical pharmacology, pharmacokinetics, and toxicology studies. Pivotal studies were conducted under Good Laboratory Practice (GLP) via the intravenous (iv) and subcutaneous (sc) routes of administration with once-weekly dosing for up to 6 months.

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

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

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

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

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, 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 of fremanezumab based on the overall toxicological data profile and adequate safety margins.

In a GLP embryo-fetal developmental toxicity 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 embryo-fetal developmental toxicity 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 0 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 support the safe repeated (monthly) administration of fremanezumab in human subjects for the duration of the Phase 2 proof-of-concept (3 months) study.

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 [redacted]

[redacted]

1.2.2.1. Clinical Pharmacology Studies

A total of 118 healthy subjects received fremanezumab across 6 completed Phase 1 studies in doses ranging from 0.2 through 2000 mg. Studies included 2 single-ascending-dose pharmacokinetic and pharmacodynamic studies in healthy men (Studies B0141001 and B0141002); a 2-cohort, placebo-controlled crossover study to examine the acute effects of administration of fremanezumab on capsaicin flare response in healthy men (Study B0141006); a parallel-group, repeat-dose study of fremanezumab in healthy subjects (Study B0141007); a single-dose study evaluating the safety, tolerability, and pharmacokinetics of doses up to 2000 mg administered iv in healthy women (Study LBR-101-008 [formerly referred to as Study B0141008]); and a study assessing the safety, tolerability, absolute bioavailability, and pharmacokinetics of single iv or sc doses of fremanezumab in healthy subjects (Study LBR-101-011).These Phase 1 studies were analyzed using the original bioanalytical method that has since been determined to underestimate measured plasma concentrations compared to the current validated assay. In those analyses, fremanezumab pharmacokinetics appeared linear over the dose range from 100 to 2000 mg with C_{max} and AUC generally increasing in proportion to the dose.

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

The pharmacokinetics (non-compartmental analysis) of fremanezumab demonstrated an increase in C_{max} and AUCs values slightly greater than dose proportionality over sc dose range of 225 to 900 mg. Median time to maximum observed concentration (t_{max}) values generally occurred 5 to 7 days post sc doses. Mean values for apparent volume of distribution (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 body 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 was similar for healthy Japanese and Caucasian subjects. Comparison of exposure parameters (C_{max} and $AUC_{0-\infty}$) from Study 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 LBR-101-011 study. The main reason for the difference in exposure appears to be the bioanalytical method used in the plasma sample analysis.

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 [redacted] and no serious adverse events considered

related to the investigational medicinal product (IMP) have been reported for the [redacted] 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 [redacted] endpoints also showed fremanezumab to be superior to placebo.

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

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

Infusion-related reaction and drug hypersensitivity were also identified as adverse drug reactions. To date, 1 subject who received fremanezumab iv had a non-serious infusion-related reaction and 1 patient who received fremanezumab via the sc route had a non-serious event of drug hypersensitivity. Both events resolved following IMP discontinuation and treatment with

diphenhydramine and methylprednisolone. Neither of these identified risks is considered important risks.

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

1.3.2. Overall Benefit and Risk Assessment for This Study

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary and Secondary Study Objectives and Endpoints

The primary and secondary study objectives and endpoints are:

Objectives	Endpoints
The **primary objective** of the study is to evaluate the efficacy of fremanezumab administered subcutaneously (sc) in adult patients with posttraumatic headache (PTH).	The **primary efficacy endpoint** is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.

Objectives	Endpoints
A **secondary objective** is to evaluate the efficacy of fremanezumab administered sc in adult patients with PTH.	The **secondary efficacy endpoints** are: • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period of treatment with the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (visit 2) in disability score, as measured by the 6-item Headache Impact Test (HIT-6) at week 12 after the first dose of the IMP • mean change from baseline (visit 2) in the assessment of patient satisfaction, as measured by the Patient Global Impression of Change scale, at 4, 8, and 12 weeks after the first dose of the IMP

Objectives	Endpoints
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered sc in adult patients with PTH compared with placebo and during the open-label period.	The **safety and tolerability endpoints** are: • occurrence of adverse events during the study • clinically significant changes in physical examinations, including body weight • clinical laboratory (serum chemistry, hematology and coagulation, and urinalysis) test results at each visit • vital signs (blood pressure, respiratory rate, body temperature, and pulse) measurements at each visit Note: Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity. • 12-lead electrocardiogram (ECG) findings at each visit • use of concomitant medication during the study • number (%) of patients who did not complete the study (day 168,end-of-study [EOS]) • number (%) of patients who did not complete the study due to adverse events • local tolerability at the injection site (ie, erythema, induration, ecchymosis, and pain) at the following time points postdose: day 0, day 28, and day 56 • hypersensitivity reaction assessment • Columbia Suicide Severity Rating Scale (C-SSRS)
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).

ADA=antidrug antibody; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; HIT-6=6-item Headache Impact Test; IMP=investigational medicinal product; PTH= posttraumatic headache; sc=subcutaneous.

2.1.1. Justification of Primary Endpoint

For this study of patients with PTH, the primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP. A headache day is defined as a day when a patient reports a headache of at least moderate severity. This measure allows the use of a relatively simple headache diary.

[redacted]

3. STUDY DESIGN

3.1. General Study Design and Study Schematic Diagram

This is a multicenter, randomized, proof-of-concept, double-blind, placebo-controlled, parallel-group study, including an open-label period, evaluating the efficacy and safety of 1 subcutaneous dose regimen of fremanezumab in adult patients with PTH. The study will consist of a screening visit, a baseline period, a double-blind treatment period lasting approximately 12 weeks, and an open-label period lasting approximately 12 weeks.

The total duration of patient participation in the study is planned to be approximately 28 weeks.

Patients will complete a screening visit (visit 1) after providing informed consent, and eligible patients will enter a baseline period lasting approximately 4 weeks (28+3 days), during which time they will enter their baseline PTH information into a daily electronic headache diary. Patients meeting eligibility requirements will be randomly assigned to 1 of 2 treatment groups with fremanezumab or placebo in a 1:1 ratio. Treatment assignment will take place with stratification based on the duration of the patient's history of PTH (<12 months and ≥12 months duration).

Screening results will be reviewed for eligibility, additional baseline assessments will be administered, and the first treatment administration will occur at visit 2. Patients will return to the study center approximately every 4 weeks (visit 3 and visit 4) for a continuation of the blinded treatment administered sc; for safety and efficacy assessments; and for blood and urine sampling for pharmacokinetics, immunogenicity, and biomarker analysis. At visit 5, all patients will proceed directly to an open-label treatment phase, with fremanezumab administered sc. Patients will then return to the study center approximately every 4 weeks (visits 6 and 7) for continued open-label treatment and safety tolerability and efficacy assessments. Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP.

A database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.

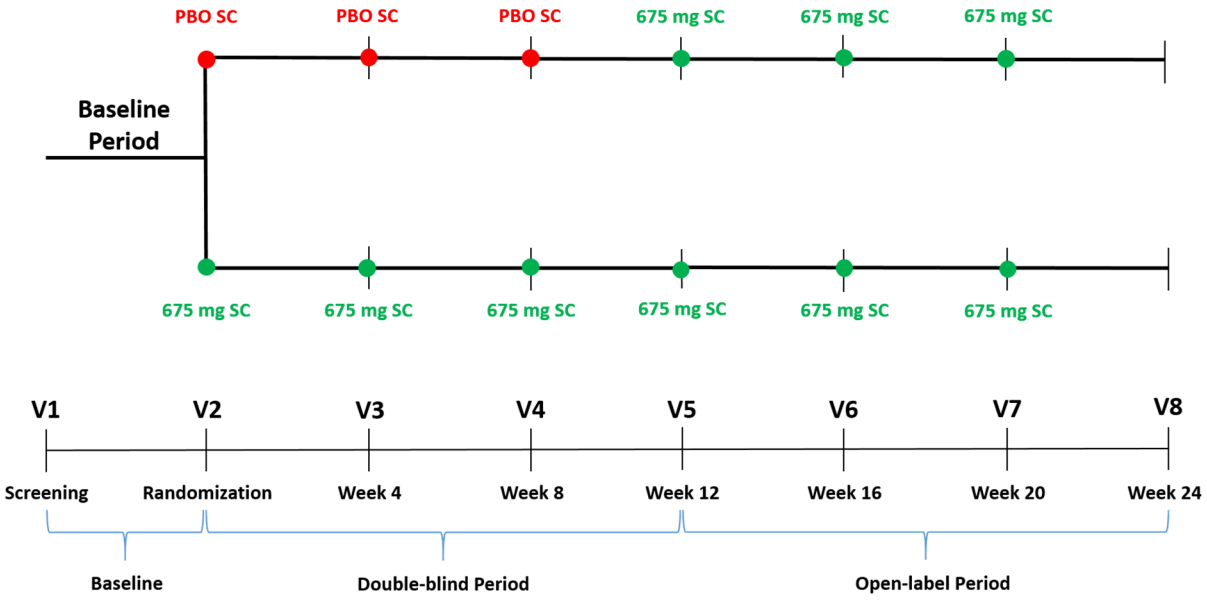
Patients who complete all scheduled visits will have procedures and assessments performed at visit 8. Patients who withdraw from the study before completing either the double blind or the open label treatment phases will have visit 8 procedures and assessments performed at their final visit. For all patients in the study, the end-of-treatment visit (visit 8) is defined as the final visit of the study and the conclusion of all study activities for the patient; patients will not receive any further treatments with IMP and will be treated according to guidelines and treating physicians' discretion.

The EOS is defined as the last safety visit. However, a final database lock will occur following the end-of-treatment visit (visit 8) of the last patient for analysis of the study data.

The total duration of the study will be approximately 2 years from Q4 of 2017 until approximately Q2 of 2020.

The study schematic diagram is presented in Figure 1.

Figure 1: Overall Study Schematic Diagram



PBO=placebo; SC=subcutaneous; V=visit.

3.2. Planned Number of Patients and Countries

The total number of patients planned was 172 (86 patients per treatment group). Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.

The study is planned to be conducted in the United States in approximately 32 study centers. The study is expected to be executed between the period of Q4 2017 and Q2 2020.

3.3. Justification for Study Design and Selection of Population

There are no evidence-based treatment guidelines for PTH management; however, expert opinion has suggested treating PTH using primary headache disorder treatment recommendations according to its type (Lucas 2015). The features of PTH most often resemble those of migraine, therefore, it is reasonable that the study design follows the recommendations of the International Headache Society (IHS) guidelines for controlled trials of drugs in migraine (Lipton et al 1995), which specify parallel-group, placebo-controlled studies (IHS 2013).

The study population will be composed of male and female patients, aged 18 to 70 years, inclusive, with a history of PTH (as defined by International Classification of Headache Disorders 3rd revision [ICHD-3] (beta version) criteria) (IHS 2013). This will include patients with headache attributed to mild, traumatic injury of the head or headache attributed to whiplash.

PTH is a headache with >1 month duration attributed to mild head injury: Glasgow Coma Scale (GCS) score of 13 to 15, loss of consciousness less than 30 minutes, duration of posttraumatic amnesia of <24 hours, and 2 or more other symptoms suggestive of mild traumatic brain injury (ie, nausea, vomiting, visual disturbances, dizziness and/or vertigo, and impaired memory and/or concentration).

Persistent headache attributed to whiplash (with or without neck pain) is a headache that has developed within 7 days after the whiplash and with >1 month duration.

Traumatic injury to the head is defined as a structural or functional injury resulting from the action of external forces on the head. These include striking the head with or the head striking an object, penetration of the head by a foreign body, forces generated from blasts or explosions.

The duration of posttraumatic amnesia is defined as the time between head injury and recovery of memory of current events and those occurring in the last 24 hours.

Whiplash is defined as sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

PTH is a common secondary headache disorder that negatively affects a patient's quality of life, in which a significant unmet medical need for treatment exists.

3.4. Stopping Rules for the Study

During the conduct of the study, serious adverse events will be reviewed (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 if any of the following conditions occur:

- New toxicological or pharmacological findings or safety issues invalidate the earlier positive benefit-risk assessment.
- Development of the IMP is discontinued.

A patient may discontinue participation in the study at any time for any reason (eg, lack of efficacy, withdrawal of consent, 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 Section 10, noncompliance, or adverse event). In addition, patients with positive C-SSRS findings or abnormal hepatic laboratory values may meet criteria for discontinuation as summarized in Appendix I.

3.5. Schedule of Study Procedures and Assessments

Study procedures and assessments with their time points are presented in Table 1. 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 H.

Table 1: Study Procedures and Assessments

Study period	**Pretreatment (including screening visit and baseline period)**	**Double-blind treatment period (visit/day or week)**			**Open-label period (visit/day or week)**			
Visit number	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[b]**
Day and allowed time windows	**Day -28 to -1 (+3 days)**	**Day 0±3 days**	**Day 28±3 days**	**Day 56± 3 days**	**Day 84±3 days**	**Day 112 ±3 days**	**Day 140±3 days**	**Day 168±3 days**
Procedures and assessments	**Screening**	**Randomization Week 0 Dose 1**	**Week 4 Dose 2**	**Week 8 Dose 3**	**Week 12 Dose 4**	**Week 16 Dose 5**	**Week 20 Dose 6**	**Week 24 EOT/EOS/ET**
Informed consent	X							
Inclusion and exclusion criteria	X	X						
Assign randomization/treatment number		X						
Medical and psychiatric history	X							
Prior medication and treatment history[c]	X							
Record demographic characteristics	X							
Adverse events inquiry[d,e,f]	X	X	X	X	X	X	X	X
Concomitant medication inquiry[f]	X	X	X	X	X	X	X	X
Clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis)[g]	X	X	X	X	X	X	X	X
Full physical examination[h]	X	X			X			

Study period	**Pretreatment (including screening visit and baseline period)**	**Double-blind treatment period (visit/day or week)**			**Open-label period (visit/day or week)**			
Visit number	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[b]**
Day and allowed time windows	**Day -28 to -1 (+3 days)**	**Day 0±3 days**	**Day 28±3 days**	**Day 56± 3 days**	**Day 84±3 days**	**Day 112 ±3 days**	**Day 140±3 days**	**Day 168±3 days**
Procedures and assessments	**Screening**	**Randomization Week 0 Dose 1**	**Week 4 Dose 2**	**Week 8 Dose 3**	**Week 12 Dose 4**	**Week 16 Dose 5**	**Week 20 Dose 6**	**Week 24 EOT/EOS/ET**
Electrocardiography[i]	X	X	X	X	X	X	X	X
Vital signs measurement[j, f]	X	X	X	X	X	X	X	X
Serum β-HCG test for women of childbearing potential[k]	X				X			X
Urine pregnancy test[k]		X	X	X				X
FSH[l]	X							
Inform patients of study restrictions and compliance requirements	X							
Review study compliance[f]		X	X	X	X			
Complete electronic headache diary[m]	X	X	X	X	X			
Review electronic headache diary[f]		X	X	X	X			
Blood samples for plasma concentration of IMP[n]		X	X	X	X	X	X	X
Blood samples for serum ADA concentration[o]		X	X		X			X

Study period	**Pretreatment (including screening visit and baseline period)**	**Double-blind treatment period (visit/day or week)**			**Open-label period (visit/day or week)**			
Visit number	**V1[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[b]**
Day and allowed time windows	**Day -28 to -1 (+3 days)**	**Day 0±3 days**	**Day 28±3 days**	**Day 56± 3 days**	**Day 84±3 days**	**Day 112 ±3 days**	**Day 140±3 days**	**Day 168±3 days**
Procedures and assessments	**Screening**	**Randomization Week 0 Dose 1**	**Week 4 Dose 2**	**Week 8 Dose 3**	**Week 12 Dose 4**	**Week 16 Dose 5**	**Week 20 Dose 6**	**Week 24 EOT/EOS/ET**
Blood collection for biomarker analysis[p]		X		X	X	X	X	X
Urine collection for biomarker analysis		X		X	X			X
Saliva sample for biomarker analysis		X	X	X	X	X	X	X
HIT-6 questionnaire		X			X	X	X	X
PHQ-2/PHQ-9[q]	X							X
SF-12 questionnaire		X			X	X	X	X
SCAT-3 questionnaire		X			X			X
PGIC questionnaire		X	X	X	X	X	X	X
C-SSRS[r, f]	X	X	X	X	X	X	X	X
Administration of IMP[s]		X	X	X	X	X	X	
Injection site assessments[t]		X	X	X	X	X	X	
Hypersensitivity/anaphylaxis[u]		X	X	X	X	X	X	
Special Protocol Headache questionnaire[v]					X			X

[a] Patients will complete a screening visit and a baseline period lasting 28 days (+3 days). 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] EOS is defined as the last safety visit (V8).
[c] The collection of prior medications is limited to those medications administered within 3 months before screening (V1).
[d] Adverse events will be recorded from the time informed consent is obtained through the EOS participation. Adverse Events Inquiry should take place both predose and postdose for visits 2 through 7.
[e] Patients will be assessed for anaphylaxis and severe hypersensitivity reaction during and after administration of the IMP.
[f] Procedures for unscheduled visits.
[g] Currently menstruating information (yes, no, or not applicable) will be collected prior to blood and urine collection for laboratory tests for all females.
[h] Height will be measured only at the screening visit.
[i] Electrocardiograms (12-lead) will be performed in triplicate with approximately 1 to 5 minutes between recordings before blood draws and administration of questionnaires.
[j] Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.
[k] Serum β-HCG and urine pregnancy tests are required for women of childbearing potential only.
[l] The FSH test is required for postmenopausal women only.
[m] Patients will enter headache days of any severity (mild, moderate, or severe), their duration, and prescription medication use into the electronic diary application daily throughout the pretreatment period and double-blind treatment periods. Eligible patients will upload the application to their own device or use the provisioned device and will be trained in its use and compliance requirements on the day of screening (visit 1). Patients will be asked to return the provisioned electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center.
[n] Blood samples for pharmacokinetic analysis (4 mL) will be collected prior to dosing at visit 2 (baseline). At each visit thereafter, a single blood sample for pharmacokinetic analysis will be collected prior to dosing, where applicable.
[o] Blood samples for serum ADA assessment (5 mL) will be collected prior to dosing at each applicable visit and will also be collected upon observation of any anaphylaxis or severe hypersensitivity reaction.
[p] Blood for further biomarker analyses will be collected after blood collection for pharmacokinetic and immunogenicity analyses as follows: 6 mL for serum, 6 mL for plasma, and 6.5 mL for PAXgene® RNA.
[q] Patients will first complete the PHQ-2. If the PHQ-2 is positive (ie, a score of ≥3), they will complete the PHQ-9.
[r] The C-SSRS Baseline/Screening version will be completed at visit 1, and the Since Last Visit version will be completed at all other subsequent visits, including unscheduled visits.
[s] Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL) at visit 2 (randomization), visit 3 (week 4), visit 4 (week 8), visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20). Patients randomized to placebo will receive placebo administered as 3 sc injections (1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).
[t] Patients will be assessed for injection site erythema, injection site induration, injection site ecchymosis, and injection site pain immediately (+10 minutes) and 1 hour (±15 minutes) after completion of each IMP administration. If a patient has severe injection site induration, injection site erythema, injection site ecchymosis, or injection site pain at 1 hour after completion of IMP administration, the patient will be reassessed 3 hours (±15 minutes) after IMP administration and hourly thereafter until the reaction is of moderate or less severity.
[u] Patients will be assessed for severe hypersensitivity/anaphylaxis reaction during and after administration of the IMP. Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.
[v] Patients will complete the Special Protocol Headache questionnaire for visits 5 and 8 following all other procedures at visits 5 and 8. Patients will be instructed to return the electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire.

ADA=anti-drug antibodies; β-HCG=beta-human chorionic gonadotropin; CRF=case report form; C-SSRS=Columbia Suicide Severity Rating Scale; EOS=end of study; EOT=end of treatment; ET=early termination; FSH=follicle-stimulating hormone; HIT-6=6-item Headache Impact Test; IMP=investigational medicinal product; PGIC=Patient Global Impression of Change; PHQ-2=2-item Patient Health Questionnaire; PHQ-9=9-item Patient Health Questionnaire; RNA=ribonucleic acid; sc=subcutaneous; SCAT-3=Sport Concussion Assessment Tool 3rd edition; SF-12=12-item Short-Form Health Survey; V=visit.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective waivers (exceptions) from study inclusion and exclusion criteria to allow patients to be randomized/enrolled are not granted by Teva (Appendix C).

Changes to inclusion or exclusion criteria are indicated below and detailed in Section 16.

4.1. Patient Inclusion Criteria

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

a. The patient is capable of giving signed informed consent as described in Appendix C, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

b. The patient is a man or woman 18 to 70 years of age, inclusive.

c. The patient has a body weight ≥45 kg.

d. Traumatic injury to the head has occurred, defined as a structural or functional injury resulting from the action of external forces. These include striking the head with or the head striking and object, penetration of the head by a foreign body, forces generated from blasts or explosions; or whiplash has occurred, defined as sudden and inadequately restrained acceleration/deceleration movements of the head with flexion/extension of the neck. Whiplash may occur after either high or low impact forces.

e. The patient has a diagnosis of PTH as per the ICHD-3 (beta version) criteria:

   – Headache is reported to have developed within 7 days after one of the following:

      ○ mild traumatic injury to the head

      ○ regaining of consciousness following the injury to the head

      ○ discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head

   In addition, the following criteria should be met:

   – Headache persists for >1 month after injury to the head

f. During the baseline period, the patient has at least 8 headache days of at least moderate severity, defined as a day when a patient reports at least 4 hours of headache (not necessarily consecutive) and at its worst at any point has at least moderate severity; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity).

g. The patient demonstrated compliance with the electronic diary during the baseline period by entry of headache data at a minimum of 75% compliance.

h. The patient is not using preventive medications for headache (presented in Appendix F) (ie, at least 5 half-lives have passed since last use) or is using them in

a dose and regimen that have been stable for at least 2 months prior to beginning the baseline period.

i. Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening and a negative urine pregnancy test at baseline, are sterile, or postmenopausal. Definitions of sterile and postmenopausal are given in Appendix D.

j. Women of childbearing potential (WOCBP) whose male partners are potentially fertile (ie, no vasectomy) must use highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 weeks after the last IMP administration. Further details are included in Appendix D.

k. Men must be sterile or, if they are potentially fertile or reproductively competent (ie, not surgically or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, a condom for the duration of the study and for 30 weeks after the last IMP administration. Further details are included in Appendix D.

l. Definitions of WOCBP, sterile and postmenopausal women, male contraception, and highly effective birth control methods, including examples, are given in Appendix D.

4.2. Patient Exclusion Criteria

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

a. The patient has a previous history of brain imaging showing evidence of intracerebral hemorrhage, subdural or epidural hematomas, or subarachnoid hemorrhage as a consequence of the traumatic head injury. Brain images with structurally insignificant changes, as discussed and approved by the sponsor, will be reviewed by the sponsor on a case-by-case basis.

b. The patient has PTH attributed to craniotomy.

c. The patient has whiplash and subsequent headache but no history of head injury or concussion.

d. The patient has an existing headache history prior to the head trauma, unless the patient reports a significant worsening of at least 50% in the frequency and/or severity of the headaches and in the opinion of the investigator, the patient fulfills criteria for PTH.

e. The patient is using analgesic medications containing opioids (including codeine) or a barbiturate on average more than 15 days per month.

f. The patient has participated in another study of an IMP (or a medical device) within the previous 30 days (or 90 days for biologics) or 5.5 half-lives, whichever is longer, of the IMP or is currently participating in another study of an IMP (or a medical device) prior to screening.

g. The patient has had exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab, and fremanezumab) during the 6 months prior to the day of the screening visit.

h. The patient is currently being treated with onabotulinumtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the 3 months prior to the screening visit.

i. The patient has been implanted with any electronic devices for headache prevention during the 3 months prior to the screening visit or is currently using any implanted or externally applied stimulator or device.

j. The patient has been treated with a nerve block for head and/or neck pain during the 3 months prior to the screening visit.

k. The patient has a known hypersensitivity to any components of the IMPs stated in this protocol.

l. The patient has a history or presence of other medical illness that, in the opinion of the investigator indicates a medical problem that would preclude study participation.

m. The patient is a pregnant or lactating woman or plans to become pregnant during the study.

n. The patient has clinically significant hematological, cardiac, renal, endocrine, pulmonary, gastrointestinal, genitourinary, neurologic, hepatic, or ocular disease or has any clinically significant uncontrolled medical condition (treated or untreated) at the discretion of the investigator.

o. The patient has any psychiatric condition or evidence of significant active or unstable psychiatric disease that, in the opinion of the investigator, could jeopardize or would compromise the patient's ability to participate in this study.

p. The patient has major depression as assessed by the 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9) at screening. Any patient with a score ≥15 should be considered to have major depression and should be referred for appropriate treatment. Patients with lower scores (5 to 14) may also have major depression, and they should be carefully evaluated by the investigator for the presence of additional symptoms.

q. The patient has a history of alcohol abuse or recreational drug abuse or at the discretion of the investigator is suspected of abusing alcohol or recreational drugs.

r. The patient has any lifetime history of suicidal behaviors (suicide attempts, interrupted attempts, aborted attempts, suicidal ideation, or preparations for suicide).

s. The patient fulfills any of the following criteria:

   – mentally or legally incapacitated or unable to give consent for any reason

   – in custody due to an administrative or a legal decision, under tutelage, or being admitted to a sanitarium or social institution

   – in current litigation for any civil or criminal offense

- in current, ongoing or future litigation for the life of the study, relating to headaches, trauma or injury to the brain
- unable to be contacted in case of emergency

t. The patient has any other condition, which, in the opinion of the investigator, makes the patient inappropriate for inclusion in the study

4.3. Withdrawal Criteria and Procedures for the Patient

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

1. Patient withdraws consent or requests discontinuation from the study for any reason.
2. Patient develops an illness that would interfere with his/her continued participation.
3. Patient is noncompliant with the study procedures and assessments or administration of IMPs in the opinion of the investigator.
4. Patient takes prohibited concomitant medications as defined in this protocol.
5. A female patient has a confirmation of pregnancy during the study from a positive pregnancy test.
6. The sponsor requests withdrawal of the patient.
7. Patient experiences an adverse event or other medical condition, which indicates to the investigator that continued participation is not in the best interest of the patient.
8. Patient scores a 5 on the C-SSRS assessment.

Due to over-enrollment, meaning that the total number of patients that may be recruited for the study or when the site enrollment limit has been reached, the sponsor may decide to cancel patient participation in the study, either because they volunteered to withdraw or because they are one of the last patients to have been screened. Therefore, they will not be permitted to be randomized. The patient will be reimbursed for reasonable transportation, parking and meal costs, if necessary. In case of cancellation, the patient should discuss with their physician options for appropriate treatment.

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 from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study or discontinuation from the IMP.

See Appendix E 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 the reason for withdrawal from the study or discontinuation from IMP is an adverse event and/or clinically significant abnormal laboratory test result, monitoring will be continued as

applicable (eg, until the event has resolved or stabilized, until the patient is referred to the care of a healthcare professional, or until a determination of a cause unrelated to the IMP or study procedure is made). The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the adverse events page and the relevant page of the CRF will be completed at that time.

If a patient is withdrawn from the study for multiple reasons that also include 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," 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 the reason for withdrawal. If a patient withdraws consent, every attempt should be made to determine the reason. The reason for and date of withdrawal from the study must be recorded on the source documentation and transcribed to the CRF.

All assessments should be performed at the early withdrawal visit according to the protocol (Appendix H).

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 by 2 different methods (eg, phone, text message, email, or certified letter). In the case of patients lost to follow-up, attempts to contact the patient must be recorded on the source documentation.

4.4. Replacement of Patients

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

4.5. Rescreening

Patients who historically screen-failed or have currently failed screening as a result of the following previous criteria will be rescreened if both conditions apply:

- headache persists for >1 month after injury to the head
- e-diary compliance level of at least 75%

A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again unless approved by the sponsor on a case-by-case basis.

Patients enrolled after rescreening will be given a new patient identification number.

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 serious adverse events.

5. TREATMENTS

5.1. Investigational Medicinal Products Used in the Study

Investigational medicinal product is defined as the test IMP and placebo IMP. Details of the test and placebo IMPs are presented in Table 2.

Table 2: Investigational Medicinal Products Used in the Study

IMP name	Fremanezumab	Placebo IMP
Company-assigned number	Fremanezumab (formerly TEV-48125, LBR-101, PF-04427429, or RN307)	Not applicable
Product configuration	Prefilled syringes	Prefilled syringes
Unit dose strength(s)/Dosage level(s)	For sc administration: 2.25 mL prefilled syringes (1.5 mL deliverable volume each) at a nominal concentration of 150 mg/mL fremanezumab	For sc administration: 2.25 mL prefilled syringes (1.5 mL deliverable volume each) with the same vehicle and excipients as those for the active injections
Route of administration	sc injection fremanezumab will be administered by qualified study personnel who will retrieve the appropriately numbered kit containing the prefilled syringes.	sc injection Placebo will be administered by qualified study personnel who will retrieve the appropriately numbered kit containing the prefilled syringes.
Dosing instructions	**Arm A:** The contents of three prefilled syringes, each containing fremanezumab (225 mg/1.5 mL) injections sc at visit 2, visit 3 and visit 4	**Arm B:** The contents of three prefilled syringes, each containing 1.5 mL placebo injections sc at visit 2, visit 3 and visit 4
Packaging	Fremanezumab will be contained in uniquely numbered kits and stored refrigerated at 2°C to 8°C at the investigational center.	Placebo will be contained in uniquely numbered kits and stored refrigerated at 2°C to 8°C at the investigational center.
Manufacturer	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, PA 19380

IMP=investigational medicinal product; sc=subcutaneous.

5.1.1. Test Investigational Medicinal Product

Fremanezumab is a humanized IgG2a/kappa monoclonal antibody derived from a murine precursor. Fremanezumab for PTH is being developed for sc administration.

Additional details may be found in Table 2 and the IB for fremanezumab.

5.1.1.1. Starting Dose and Dose Levels

Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8). Patients will then enter the open-label period of the study, where they will receive

675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20).

5.1.2. Placebo Investigational Medicinal Product

The placebo will consist of the same vehicle and excipients as those for fremanezumab. See Table 2 for additional details. Patients randomized to placebo will receive placebo administered as 3 sc injections (1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8).

5.2. Preparation, Handling, Labeling, Storage, and Accountability for IMPs

5.2.1. Preparation of Investigational Medicinal Product

Fremanezumab or placebo will be provided in prefilled syringes contained in uniquely numbered kits and stored as described below. At the time of each study visit, the interactive response technology (IRT) will be queried and investigational center personnel will retrieve the appropriately numbered kit(s). Kit numbers will be automatically entered into the database through IRT.

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 2.25-mL syringe in each visit kit must be injected sc for dosing to be considered complete. Refer to the pharmacy manual for additional details regarding recommended sc injection sites.

5.2.2. Storage and Security

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

The IMPs (fremanezumab and placebo IMP) must be stored refrigerated at 2°C to 8°C, protected from light. The investigational center must have a process for monitoring IMP storage temperature.

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

5.2.3. 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.

5.2.4. 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 (CFR) or national and local regulations and used in accordance with this protocol.

Only patients enrolled in the study may receive IMPs, and only qualified 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. Prefilled syringes should never be used partially. Empty syringes should be destroyed at the investigational center after reconciliation is performed. If the investigational center does not have the capability to destroy the empty syringes, they should be sent back to the sponsor. Unused prefilled syringes of IMP will be returned to the sponsor or designee.

Additional information pertaining to the preparation, handling, labeling, storage, and accountability for the IMP used in this study can be found in the Pharmacy manual.

5.3. Justification for Investigational Medicinal Products

5.3.1. Justification for Dose of Test Investigational Medicinal Product

The fremanezumab dose and dosing regimen to be evaluated in this double-blind study was selected on the basis of animal pharmacodynamic and pharmacokinetic data, 7 pharmacokinetic/safety studies in healthy volunteers, 5 safety/efficacy studies in patients with migraine, 2 safety/efficacy studies in patients with cluster headache and population pharmacokinetic and pharmacokinetic/pharmacodynamic modeling and simulations.

The dose of 675 mg sc monthly for 3 months may provide evidence of the efficacy of fremanezumab in patients with PTH (ie, proof-of-concept). The dose regimen used in this study will allow the exploration of the time of onset of action and assist in defining dose regimen(s) for Phase 3 studies in the PTH population. Model and simulations suggest that C_{max} is the most significant pharmacokinetic parameter in the efficacy of fremanezumab (in migraine). The planned dose regimen in this Phase 2 study will provide practicality and feasible maximal exposure while applying sc doses.

In addition, fremanezumab 675 mg sc monthly for 3 months was also administered in a phase 2 study with episodic migraine patients. The results of this study showed the dose to be effective, safe, and well tolerated by these patients. Moreover, fremanezumab was well tolerated and generally safe with single iv doses up to 2000 mg in healthy volunteers.

5.3.2. Justification for Use of Placebo Investigational Medicinal Product

A placebo-controlled design is appropriate given the purpose and objectives of this clinical study. Inclusion of a placebo-control group is consistent with the IHS guidelines for controlled trials of drugs in PTH (IHS 2013).

5.4. Treatment After the End of the Study

Patients will return to the investigational center approximately 24 weeks following administration of the first dose of IMP for safety evaluation. No treatment is planned by the sponsor after completion of the study. Patients should be treated with standard of care after withdrawal from or termination of the study, as appropriate.

5.5. Restrictions

Patients will be required to comply with the following restrictions:

5.5.1. Activity

Patients must remain at the investigational center for safety observation at least 60 minutes after administration of IMP or according to medical judgment.

5.5.2. Blood Donation

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

5.5.3. Pregnancy

Restrictions in regard to pregnancy and required associated laboratory values (ie, serum and urine β-HCG tests) are provided in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively). Restrictions in regards to contraception methods are given in Appendix D.

5.6. Prior and Concomitant Medication or Therapy

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

For daily-prescribed medications and preventative treatments, patients must be on a stable dose and regimen for at least 2 weeks prior to screening and maintained throughout the study until the completion of visit 8.

The following medications will be prohibited during this study:

- analgesic medications containing opioids (including codeine) if used for more than 15 days per month
- a barbiturate if used for more than 15 days per month

- CGRP antibody or any antibody to the CGRP receptor
- OnabotulinumtoxinA (eg, Botox, Dysport, Xeomin)
- devices for headache prophylaxis
- nerve block for head and/or neck

All patients will be questioned about concomitant medications at each study visit. Prohibited medications are provided in Appendix F.

5.7. Procedures for Monitoring Patient Compliance

The investigator will be responsible for monitoring patient compliance. A check of compliance with IMP intake will be performed during each visit after the IMP has been administered; and IMP accountability records will be completed.

If the investigator or the sponsor determines that the patient is not in compliance with the study protocol, the investigator and the sponsor should determine whether the patient should be withdrawn from the study.

Exposure to IMP will be assessed as required.

5.8. Randomization and Blinding

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

Following the screening period, patients will be randomized if they have 8 or more headache days (defined as a day when a patient reports at least 4 hours of headache [not necessarily consecutive] and at its worst at any point has at least moderate severity; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache [regardless of duration or severity]) during the baseline period. Electronic diary completion must be at least 75% during the baseline period for randomization eligibility and at least 75% during the double-blind treatment period, during which the patient cannot miss more than 7 days of recording nor more than 4 days in a row. Randomization will be performed using electronic IRT. Patients will be randomly assigned with stratification based on the PTH onset (<12 months and ≥12 months since the brain injury) in a 1:1 ratio to receive fremanezumab or placebo, as assigned by the IRT. The IRT will manage initial IMP supply, maintenance of adequate IMP supplies at the investigational centers, and study randomization centrally.

5.9. Maintenance of Randomization and Blinding

5.9.1. Maintenance of Randomization

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

After all patients have completed visit 5 and an unblinding request from the Teva statistician has been received, the third-party vendor will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure.

5.9.2. Blinding and Unblinding

Blinded pharmacokinetic data may be assessed during the study. Personnel responsible for sample bioanalysis (pharmacokinetics and immunogenicity) will be provided with the randomization code to facilitate the analysis. However, the personnel responsible for bioanalysis and pharmacokinetic 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.These individuals will not be involved in the conduct of any study procedures or assessment of any adverse events.

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

When a blind is broken, the patient will be withdrawn from the study and the event will be recorded on 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. Assignment of IMP 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 (GPSP) may independently request that the blind 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 in the analysis and reporting of the data.

IMP assignments will be unblinded after all patients have completed visit 5.

5.9.3. Data Monitoring Committee

There will be no Data Monitoring Committee for this study.

5.10. Total Blood Volume

The total blood volume to be collected for each patient in this study is approximately 210 mL. Details are provided in Appendix G.

6. ASSESSMENT OF EFFICACY

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

6.1. Electronic Diary Application

Efficacy endpoints related to PTH will be derived from data collected daily using an electronic diary application uploaded by the patient onto their own device. Should a patient not have a compatible device, the investigational center may supply a provisioned device. Eligible patients will receive comprehensive training at screening from the investigational center personnel on the use of the electronic diary application, including the requirement for timely and daily completion of the electronic diary.

On each day throughout the baseline and double-blind treatment periods, the patient will be asked to record in the electronic diary data regarding the headache. Patients will be asked a series of questions about the headache, for example, whether or not a headache was present (yes or no), the peak severity of the headache (mild, moderate, or severe), and the duration of the headache (did the patient have at least 4 hours [not necessarily consecutive] of headache).

If a patient fails to complete the diary for the preceding day within the allowed timeframe (up to 48 hours), the patient will not be permitted to enter the missed day's information into the electronic diary, and it will be recorded as a missed day. A check of compliance for the use of the device per protocol will be done during each visit. If the investigator or the sponsor determines that the patient is not in 75% compliance during the baseline period and 75% compliance during the active treatment period, the investigator and the sponsor should determine whether the patient should be withdrawn from the study.

6.2. Six-Item Headache Impact Test

HIT-6 is a tool used to measure the impact headaches have on a patient's normal daily life and ability to function (Kosinski et al 2003). The HIT-6 consists of 6 items, including pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress. Each item is answered on a 5-point Likert scale (6 = never, 8 = rarely, 10 = sometimes, 11 = very often, or 13 = always), which are summed to produce a total score that ranges from 36 to 78, with larger scores reflecting greater impact of headache on the daily life of the patient.

Patients will complete the HIT-6 questionnaire at the time points detailed in Table 1.

6.3. 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, including 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 questionnaire at the time points detailed in Table 1.

6.4. 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 how they feel during assigned time points compared with how they felt before receiving IMP on a 7-point scale, where 1 is “no change (or condition has worsened),” 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.”

Patients will record responses to the PGIC scale at the time points detailed in Table 1.

6.5. Special Protocol Headache Questionnaire

The Special Protocol Headache questionnaire was developed by Teva to assess patient headaches following treatment with IMP. Patients who complete the baseline period and 24-week treatment period will record responses to the Special Protocol Headache Questionnaire for visit 8 as the last procedure at the end-of-treatment visit (visit). Patients will be asked to record responses regarding their perception of the frequency and severity of headache during the prior 12 weeks of treatment with IMP, as well as the number of days of school, work, or social activities that were affected by headache during the treatment period. Patients will be instructed to return the electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire.

The time points for the Special Protocol Headache questionnaire are detailed in Table 1.

7. ASSESSMENT OF SAFETY

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, clinical laboratory test results, vital signs measurements, ECG findings, physical examination findings (including body weight measurements), injection site assessments, PHQ-2/PHQ-9 and C-SSRS scores, and use of concomitant medication.

7.1. Adverse Events

7.1.1. Definition of an Adverse Event

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

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the test IMP, 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 first 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 is defined for each patient as the time period from signature of the ICF to the end of the final study period. The final period of recording of adverse events is defined as 24 weeks after the first dose of IMP (visit 8). The period for reporting treatment-emergent adverse events is defined as the period after the first dose of IMP is administered and until the end of the final study period (visit 8).

All adverse events that occur during the defined study period must be recorded both on the source documentation and the CRF, regardless of the severity of the event or judged relationship to the test IMP. For serious adverse events and protocol-defined adverse events of special interest, the serious adverse event form must be completed and the serious adverse event or the adverse event of special interest must be reported immediately (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 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 healthcare professional; or until a determination of a cause unrelated to the test 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 both on the source documentation and the CRF.

The severity, seriousness, and relationship of each adverse event to the test IMP and study procedures, 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 one 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 (ie, injection site erythema, injection site induration, injection site ecchymosis, and injection site pain), please refer to Section 7.9.

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 3: The Relationship of an Adverse Event to the Test IMP

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 investigational medicinal product (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.

7.1.5. Serious Adverse Events

For recording of serious adverse events, the study period is defined for each patient as the time period from signature of the ICF to the end of the study period. Serious adverse events occurring in a patient after the end of the 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.

7.1.5.1. Definition of a Serious Adverse Event

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

- results in death
- is life-threatening adverse event (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe

- requires inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

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

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

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

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

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of >3× the upper limit of normal (ULN)
- total bilirubin increase of >2× ULN
- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase)
- 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 GPSP 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 but before the final study visit (visit 8) 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 GPSP.

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

- study number
- investigator and investigational center identification number
- 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
- relevant concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- relevant 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 test IMP)
  - autopsy findings (if available)
  - autopsy report if autopsy was done

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.

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

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

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

7.1.5.3.2. Sponsor Responsibility

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

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

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

7.1.6. Protocol-Defined Adverse Events Not for Expedited Reporting

Not applicable.

7.1.7. Protocol-Defined Adverse Events of Special Interest

For purposes of this protocol, the following are considered protocol-defined adverse events of special interest to be sent to the sponsor's GPSP for evaluation: ophthalmic-related adverse events of at least moderate severity, events of possible drug-induced liver injury (AST or ALT ≥3× ULN, total bilirubin ≥2× ULN, or international normalized ratio >1.5), Hy's Law events, or events of anaphylaxis and severe hypersensitivity. Refer to Appendix I for guidance regarding monitoring of patients with elevated liver function tests. Anaphylaxis and severe hypersensitivity will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al 2006) (see Appendix J). In the event of expected anaphylaxis and severe hypersensitivity, vital signs, including oxygen saturation and respiration rate, will be measured. Other assessments will be performed at the discretion of the investigator.

The process for reporting a protocol-defined adverse event of special interest is the same as that for reporting a serious adverse event (Section 7.1.5.3). These adverse events of special interest to be reported to GPSP 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 allowed on a case-by-case basis. 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.

7.2. Pregnancy

Any female patient 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 40 weeks after administration of the first dose of the IMP are to be reported immediately to the individual identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the sponsor (LSO/CRO) with the completed pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (Section 7.1.5.3).

The investigator is not required to report patients who are found to be pregnant between screening and baseline, provided no protocol-related procedures were applied.

All female patients 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, one 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 on the drug administration CRF, regardless of whether or not an adverse event occurred as a result.

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

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

7.4.1. Serum Chemistry, Hematology, and Urinalysis

Clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis) will be performed at the time points detailed in Table 1. Clinical laboratory tests will be performed using the central laboratory. Specific laboratory tests to be performed are provided in Appendix K.

7.4.2. Other Clinical Laboratory Tests

7.4.2.1. Human Chorionic Gonadotropin Tests

A serum β-HCG test will be performed for all WOCBP at screening (visit 1), and EOT or early termination (visit 8), and urine β-HCG tests will be performed for WOCBP at time points specified in Table 1. Any female patient who becomes pregnant during the study will be withdrawn. Procedures for reporting pregnancy are provided in Section 7.2.

7.4.2.2. Follicle-Stimulating Hormone Tests

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

7.4.2.3. Saliva Collection

Saliva samples (~1 mL) will be collected using a standardized protocol available in the laboratory manual at time points described in Table 1. Care should be taken to freeze (at -70°C) the properly collected saliva samples as soon as possible (3-5 minutes) after collection from the patient. For additional details see Appendix N.

7.5. Physical Examinations

Physical examinations, including height (to be obtained at the screening visit only) and weight, will be performed at the time points detailed in Table 1. A full physical examination will include

the following: general appearance, head, eyes, ears, nose, throat, chest and lungs, heart, abdomen, musculoskeletal, skin, lymph nodes, and neurological systems. 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 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 1. 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

Oxygen saturation and respiratory rate will be measured in cases of suspected anaphylaxis and severe hypersensitivity.

Before blood pressure and pulse are measured, the patient must rest in a supine or semi-erect/seated position 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 value, 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 both on the source documentation and the CRF, and monitored as described in Section 7.1.2.

7.7. Electrocardiography

A 12-lead ECG will be conducted prior to other assessments (eg, blood draws and administration of questionnaires) at the time points detailed in Table 1. The ECGs should be performed in triplicate with approximately 1 to 5 minutes between recordings after the patient has been supine for at least 5 minutes.

A qualified physician at a central diagnostic center will be responsible for interpreting all ECGs. ECGs, including those for unscheduled visits, should be performed and transmitted according to the central ECG reading instructions provided in the ECG user manual. ECG equipment will be provided to all investigational centers.

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

When potentially clinically significant findings are detected by the investigator, a cardiologist should be consulted for a definitive interpretation. Any abnormal findings assessed by the

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

7.8. Immunogenicity

Blood samples (fremanezumab-treated patients only) for serum ADA assessment will be collected at the time points detailed in Table 1. Blood samples for ADA assessment will also be collected upon observation of any severe hypersensitivity reaction (eg, anaphylaxis). Bioanalytical personnel should be made aware of anaphylaxis occurrence as soon as possible in the event that an anti-fremanezumab immunoglobulin E assay is needed.

7.9. Assessment of Local Tolerability and Pain

Injection site assessments will be performed immediately (+10 minutes) and 1 hour (±15 minutes) after administration of each dose of the IMP (Table 1). 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 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.
- Spontaneous report of local pain after the injection will be measured as described in Table 4.

Table 4: 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 erythema, induration, 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 as described in Section 7.1.

7.10. Sport Concussion Assessment Tool 3rd Edition

The SCAT-3 is a standardized tool for the evaluation of injured athletes for concussion (McCrory et al 2009). It includes 8 metrics to measure concussion symptoms, including GCS, Maddocks Score, symptom evaluation, cognitive assessment, neck examination, balance examination, coordination examination, and Standardized Assessment of Concussion delayed recall. An adapted version of the SCAT-3 tool will be used.

Patients will complete the SCAT-3 questionnaire at the time points detailed in Table 1.

7.11. Two-Item Patient Health Questionnaire/Nine-Item Patient Health Questionnaire

The Patient Health Questionnaire is a 9-item questionnaire with each item corresponding to 1 criterion of the Diagnostic and Statistical Manual for Mental Disorders 4th edition diagnostic criteria for major depressive disorder. Each of the items is scored on a scale of 0 (“not at all”) to 3 (“nearly every day”) based on the frequency of symptoms (Spitzer et al 1999). The PHQ-2 was developed from the PHQ-9 to rapidly screen for depression. The PHQ-2 and the PHQ-9 are validated measures for detecting and monitoring depression, anxiety, and somatization (Kroenke et al 2010).

Patients will complete the PHQ-2 at the screening visit (visit 1) and the end of treatment or early termination visit (visit 8). If the PHQ-2 is positive (ie, a score of ≥3), patients will complete the PHQ-9.

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

A positive finding will be defined as a score ≥4: current suicide ideation with some intent to act, but no specific plan. In the case of a positive finding, the investigator, based on his medical judgment, will determine if the patient should be seen by a mental health specialist and if the patient should continue participation in the study. If the patient scores a 5: current suicide ideation with specific plan and intent, then the patient should be discontinued from the study immediately and seen by a mental health specialist.

7.13. Concomitant Therapy or Medication

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

8. ASSESSMENT OF PHARMACOKINETICS, BIOMARKERS, AND IMMUNOGENICITY

8.1. Pharmacokinetic Assessment

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

Blood samples (approximately 4 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 1 for plasma concentration measurements of fremanezumab. The dates and times of IMP administration and the date and time of each pharmacokinetic sample will be recorded both on the source documentation and the CRF.

Samples from patients who receive IMP will be analyzed for concentration of fremanezumab using a validated method. Samples from patients who were randomized to receive placebo will not be analyzed (relevant only for double blind period). Details on sample handling, storage, shipment, and analysis are given in Appendix L.

8.2. Pharmacodynamics Assessment

Pharmacodynamics parameters are not evaluated in this study.

8.3. Immunogenicity Testing

Blood samples (approximately 5 mL) will be collected via venipuncture or indwelling catheter at the time points detailed in Table 1.

Samples from patients who receive active IMP will be analyzed for ADA using a validated method. Samples from patients who receive placebo will not be analyzed.

Details on sample handling, storage, shipment, and analysis are provided in Appendix M.

[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 CSR.

[redacted]

9.2. Analysis Sets

9.2.1. Intent-to-Treat Analysis Set

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

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

9.2.2. Full Analysis Set

The full analysis set (FAS) is a subset of the ITT analysis set including only patients who receive at least 1 dose of IMP and have at least 1 post-baseline efficacy assessment on the primary endpoint.

9.2.3. Safety Analysis Set

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

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

9.2.4. Per-Protocol Analysis Set

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

9.3. Data Handling Conventions

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

9.4. Study Population

The study population will be composed of male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by ICHD-3 [beta version] criteria).

This population will include patients with headache attributed to mild, traumatic injury of the head and patients with headache attributed to whiplash.

The ITT analysis set (Section 9.2) will be used for all study population summaries, unless otherwise specified. Summaries will be presented by treatment group and for all patients.

9.4.1. Patient Disposition

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

9.4.2. Demographic and Baseline Characteristics

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

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

9.5. Efficacy Analysis

The primary efficacy endpoint for this study will be derived from PTH data (presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.

For the purposes of this study, a PTH will be confirmed when the following situations occur:

- Headache is reported to have developed within 7 days of trauma or injury (including whiplash [with or without neck pain]), within 7 days after regaining consciousness, or within 7 days of discontinuation of medication(s) that impair ability to sense or report headache following injury to the head.

- Headache persists for >1 month after the injury (including whiplash [with or without neck pain]) to the head.

9.5.1. Primary Endpoint

The primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP. The baseline parameters for each patient will be established during the baseline period.

9.5.2. Secondary Endpoints

The secondary endpoints to further demonstrate efficacy are:

- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period of treatment with the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP
- proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP
- mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP
- mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 5- to 8 week period after the first dose of the IMP
- mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP
- mean change from baseline (visit 2) in disability score, as measured by the 6 item Headache Impact Test (HIT 6) at week 12 after the first dose of the IMP
- mean change from baseline (visit 2) in the assessment of patient satisfaction, as measured by the Patient Global Impression of Change scale, at 4, 8, and 12 weeks after the first dose of the IMP

9.5.3. Immunogenicity Endpoints

The immunogenicity endpoints are ADA incidence and characteristics (eg, titer, kinetics, and neutralizing activities).

[redacted]

[redacted]

9.5.5. Planned Method of Analysis

The FAS (Sections 9.2.2) will be used for all efficacy analyses. Summaries will be presented by treatment group.

9.5.5.1. Primary Efficacy Analysis

The primary efficacy endpoint for this study will be derived from PTH data (ie, presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) method. The model will include treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariate. A 95% confidence interval will be constructed for the least squares mean difference between the fremanezumab group and the placebo group, and the p-value will be presented.

The primary estimand for this study is defined by the following attributes:

- The target population includes male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by the ICHD-3 [beta version] criteria).
- The primary outcome measure is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP.
- The FAS will be used for efficacy analyses. FAS is a subset of the ITT analysis set and includes only patients who receive at least 1 dose of IMP and have at least 1 postbaseline efficacy assessment on the primary endpoint. In the FAS, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received.
- Treatment effect will be measured via ANCOVA method, including treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariates.

For patients assigned to active treatment who discontinue the study due to lack of efficacy, death, or adverse event, the proportion of headache days in the remainder of the analysis window will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to placebo. All other missing data for patients in either treatment group will be handled as follows:

- For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number of headache days will be calculated based on data available in that analysis window and prorated to 28 days.
- For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data. Sensitivity analyses will be conducted as defined in the statistical analysis plan.

9.5.5.2. Sensitivity Analysis

Sensitivity analysis will be conducted to explore the impact of missing data in the primary efficacy analysis. In particular, endpoints analyzed using an ANCOVA method will be analyzed

using a mixed model for repeated measures method. The details will be described in the statistical analysis plan.

9.5.5.3. Secondary Efficacy Analysis

The continuous secondary efficacy endpoints will be analyzed using an ANOVA method or a mixed-model for repeated measures. For the proportion of responders defined as 50% or more reduction from baseline in the monthly average headache days, the Cochran-Mantel-Haenszel test will be used stratified by PTH onset (<12 months and ≥12 months). For the key secondary endpoints, a 95% confidence interval will be constructed to compare the treatment effect between the fremanezumab group and the placebo group, and the p-value will be presented.

[redacted]

9.6. Multiple Comparisons and Multiplicity

Testing of statistical significance at a 2-sided alpha of 0.05 will be performed for the primary endpoint. If the primary endpoint meets statistical significance, then each of the key secondary endpoints will be tested for significance in a pre-specified order at a 2-sided alpha of 0.05. If and when any p>0.05, no further comparisons will be interpreted inferentially. Details will be presented in the statistical analysis plan.

9.7. Safety Analysis

Safety analyses will be performed on the safety analysis set (Section 9.2.3).

Safety assessments and time points are provided in Table 1.

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.

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

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 test IMP.

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 be provided as well.

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 CSR.

9.8. Tolerability Analysis

Injection site reaction assessments will be listed and summarized descriptively.

9.9. Pharmacokinetic Analysis

Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point. At the open-label period, pharmacokinetic plasma concentration results will be tabulated descriptively at each planned sampling time point treatment group.
In addition, the most appropriate population pharmacokinetic model may be developed, and covariates that may affect it will be tested for inclusion in the model. If performed, this analysis will be reported separately.

9.10. Pharmacokinetic/Pharmacodynamic Analysis

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

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

[redacted].

9.12. Pharmacogenomic Analysis

Pharmacogenomic analysis will be conducted to correlate clinical observations (pharmacokinetic, safety, efficacy, or other effects) with genotypes observed in the study. Pharmacogenomic analysis may be conducted at a later time and will be reported in a separate addendum report.

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, fremanezumab efficacy, and clinical safety will be evaluated. This analysis will be reported separately.

9.14. Planned Interim Analysis

There will be no formal interim analysis. However, a database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.

9.15. 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 CSR, 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 B 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 O for the definition of a clinical product complaint and investigator responsibilities in the management of a clinical product complaint.

11. COMPLIANCE STATEMENT

This study will be conducted in full accordance with the ICH Harmonised Tripartite Guideline for GCP E6 and any applicable national and local laws and regulations (eg, Title 21 Code of Federal Regulations [21CFR] Parts 11, 50, 54, 56, 312, and 314, Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice 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 C for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.

12. DATA MANAGEMENT AND RECORD KEEPING

See Appendix P 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 Q for information regarding the publication policy.

15. REFERENCES

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16. SUMMARY OF CHANGES TO PROTOCOL

16.1. Amendment 02 Dated 30 March 2020

The primary reason for this amendment is to revise the planned number of patients as study recruitment was discontinued at 87 patients due to challenges to enrollment. Additionally, revisions have been made to the justification of the primary endpoint, including the primary analysis method, revise the secondary endpoints, [redacted]. This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's authorized representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). 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 1 (Study Procedures and Assessments) has been revised to reflect changes described below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
TITLE PAGE (Other sections affected by this change: protocol header, Investigator Agreement, Coordinating Investigator Agreement)		
Protocol with Amendment 02 Approval Date: 30 March 2020	**Protocol with Amendment 02 Approval Date: 30 March 2020**	To update for Amendment 02
Teva Branded Pharmaceutical Products R&D, Inc. ~~41 Moores Road~~ 145 Brandywine Parkway ~~Frazer~~West Chester, Pennsylvania ~~19355~~19380 United States of America	Teva Branded Pharmaceutical Products R&D, Inc. 145 Brandywine Parkway West Chester, Pennsylvania 19380 United States of America	To update the sponsor's new address
Section 1.1 Introduction		
~~Most often t~~They can resemble a range of primary headache conditions such as ~~those of~~ migraine (ie, moderate to severe intensity, pulsating, associated nausea or vomiting, light or sound sensitivity, and worsened with activity) or tension-type headache (ie, mild to moderate intensity, non-pulsating, light or sound sensitivity, but no nausea or vomiting), or one of a number of more uncommon headache syndromes (Finkel et al 2017). ~~Consequently~~Rather, the diagnosis of PTH is largely dependent on the close temporal relationship between the trauma or injury and headache onset. PTH requires that the headache must be reported to have developed within 7 days of trauma or injury, or within 7 days of having regained consciousness, and/or ability to report pain when these have been lost following trauma or injury~~. During the first 3 months from onset, these headaches are considered acute. A PTH that continues beyond the first 3 months from onset is designated as a persistent posttraumatic headache (PPTH)~~ (IHS 2013).	They can resemble a range of primary headache conditions such as migraine (ie, moderate to severe intensity, pulsating, associated nausea or vomiting, light or sound sensitivity, and worsened with activity) or tension-type headache (ie, mild to moderate intensity, non-pulsating, light or sound sensitivity, but no nausea or vomiting), or one of a number of more uncommon headache syndromes (Finkel et al 2017). Rather, the diagnosis of PTH is largely dependent on the close temporal relationship between the trauma or injury and headache onset. PTH requires that the headache must be reported to have developed within 7 days of trauma or injury, or within 7 days of having regained consciousness, and/or ability to report pain when these have been lost following trauma or injury (IHS 2013).	

Original text with changes shown	New wording	Reason/Justification for change
The pathogenesis of PTH is ~~often unclear~~ most commonly in the absence of overt brain injury.	The pathogenesis of PTH is most commonly in the absence of overt brain injury.	
It is recommended that treatment for secondary headache types, such as PTH, be consistent with the treatment of the primary headache type it most resembles~~, in this case, migraine~~ (Lucas 2015).	It is recommended that treatment for secondary headache types, such as PTH, be consistent with the treatment of the primary headache type it most resembles (Lucas 2015).	
~~These results suggest that fremanezumab may be successful for the prevention of PTH.~~	-	
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Section 9.5.2)		
See new changes column.	The **secondary efficacy endpoints** are: • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period of treatment with the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the first 4-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 5- to 8-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the first 4-week	Criteria changed from monthly average number of headache days of any severity to headache days of at least moderate severity for the first secondary endpoint. [redacted]

Original text with changes shown	New wording	Reason/Justification for change
	period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 5- to 8 week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity during the 9- to 12-week period after the first dose of the IMP • mean change from baseline (visit 2) in disability score, as measured by the 6 item Headache Impact Test (HIT 6) at week 12 after the first dose of the IMP • mean change from baseline (visit 2) in the assessment of patient satisfaction, as measured by the Patient Global Impression of Change scale, at 4, 8, and 12 weeks after the first dose of the IMP	
Section 2.1.1 Justification of Primary Endpoint		
For this study of patients with PTH, the primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP. A headache day is defined as a day when a patient reports ~~at least 4 hours of~~ a headache ~~(not necessarily consecutive) and at its worst at any point has~~ of at least moderate severity~~; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity).~~. This measure allows the use of a relatively simple headache diary. ~~The patient will indicate the presence of headache (yes/no), its peak severity (mild/moderate/severe), its duration (<4 hours/4 hours), and whether or not prescription medication~~	For this study of patients with PTH, the primary efficacy endpoint is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP. A headache day is defined as a day when a patient reports a headache of at least moderate severity. This measure allows the use of a relatively simple headache diary.	The definition of a headache day was revised for the primary endpoint analysis to better align with measures used in patients with PTH.

Original text with changes shown	New wording	Reason/Justification for change
~~was taken to alleviate the headache daily during the baseline period to establish the baseline parameters and daily through the 12-week treatment period.~~		
[redacted]		
[redacted]	[redacted]	[redacted]

Original text with changes shown	New wording	Reason/Justification for change
	the number of headache days of at least moderate severity in patients with at least 4 hours of a headache (not necessarily consecutive) or who took a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity) during the first 4-week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity in patients with at least 4 hours of a headache (not necessarily consecutive) or who took a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity) during the 5- to 8 week period after the first dose of the IMP • mean change from baseline (baseline period) in the number of headache days of at least moderate severity in patients with at least 4 hours of a headache (not necessarily consecutive) or who took a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity) during the 9- to 12-week period after the first dose of the IMP • proportion of patients reaching at least 50% reduction from baseline (baseline period) in the monthly average number of headache days of at least moderate severity in patients with at least 4 hours of a headache (not necessarily consecutive) or who took a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity) during the 12 week period after the first dose of the IMP	

Original text with changes shown	New wording	Reason/Justification for change
Section 3.2 Planned Number of Patients and Countries		
The total number of patients planned ~~is~~was 172 (86 patients per treatment group). Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.	The total number of patients planned was 172 (86 patients per treatment group). Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.	Clarification to the sample size as study enrollment was discontinued due to challenges to recruitment prior to reaching the target sample size.
The study is planned to be conducted in the United States in approximately 32 ~~25~~ study centers. The study is expected to be executed between the period of Q4 2017 and Q2 2020.	The study is planned to be conducted in the United States in approximately 32 study centers. The study is expected to be executed between the period of Q4 2017 and Q2 2020.	Text was updated to reflect change in study centers that was made throughout protocol in protocol amendment 01, but omitted in Section 3.2, as detailed in Letter of Clarification 06.
Section 3.5 Schedule of Study Procedures and Assessments		
See new wording column	Table 1 has been modified as described below: Footnote “a” added on visit 1 column heading	Correction. Footnote “a” was inadvertently omitted from the column heading
[m] Patients will enter headache days of any severity (mild, moderate, or severe), their duration, and prescription medication use into the electronic diary application daily throughout the pretreatment period and double-blind treatment periods. Eligible patients will upload the application to their own device or use the provisioned device and will be trained in its use and compliance requirements on the day of screening (visit 1). Patients will be asked to return the provisioned ~~device~~ electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center ~~at the EOT or early termination visit (visit 5)~~.	[m] Patients will enter headache days of any severity (mild, moderate, or severe), their duration, and prescription medication use into the electronic diary application daily throughout the pretreatment period and double-blind treatment periods. Eligible patients will upload the application to their own device or use the provisioned device and will be trained in its use and compliance requirements on the day of screening (visit 1). Patients will be asked to return the provisioned electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center.	Clarification, as detailed in Letter of Clarification 06.
[o] Blood samples for serum ADA assessment (5 mL) will be collected prior to dosing at each applicable visit and will also be collected upon observation of any anaphylaxis or severe hypersensitivity reaction.	[o] Blood samples for serum ADA assessment (5 mL) will be collected prior to dosing at each applicable visit and will also be collected upon observation of any anaphylaxis or severe hypersensitivity reaction.	Clarification, as detailed in Letter of Clarification 07.

Original text with changes shown	New wording	Reason/Justification for change
[v] Patients will complete the Special Protocol Headache questionnaire for visits 5 and 8 following all other procedures at visits 5 and 8. Patients will be instructed to return the ~~provisioned devices~~ electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire ~~(visit 8)~~.	[v] Patients will complete the Special Protocol Headache questionnaire for visits 5 and 8 following all other procedures at visits 5 and 8. Patients will be instructed to return the electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire.	Clarification, as detailed in Letter of Clarification 06.
Section 4.2 Patient Exclusion Criteria		
h. The patient is ~~not~~ currently being treated with onabotulin~~m~~umtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the 3 months prior to the screening visit.	h. The patient is currently being treated with onabotulinumtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the 3 months prior to the screening visit.	Correction of a typo as patients will be excluded from the study if they are currently being treated with onabotulinumtoxinA.
Section 4.3 Withdrawal Criteria and Procedures for the Patient		
See ~~Appendix F~~Appendix E 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.	See Appendix E 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.	Correction to appendix hyperlinking, as described in Letter of Clarification 09.
All assessments should be performed at the early withdrawal visit according to the protocol (~~Appendix B~~ Appendix H).	All assessments should be performed at the early withdrawal visit according to the protocol (Appendix H).	Correction to appendix hyperlinking.
Section 5.5.3 Pregnancy		
Restrictions in regards to contraception methods are given in ~~Appendix E~~ Appendix D.	Restrictions in regards to contraception methods are given in Appendix D.	Correction to appendix hyperlinking.
Section 5.10 Total Blood Volume (Other sections affected by this change: Appendix G)		
The total blood volume to be collected for each patient in this study is approximately ~~140.5~~210 mL. Details are provided in Appendix G.	The total blood volume to be collected for each patient in this study is approximately 210 mL. Details are provided in Appendix G.	Correction to the total blood volume, as detailed in Letter of Clarification 07.
Section 6.5 Special Protocol Headache Questionnaire		

Original text with changes shown	New wording	Reason/Justification for change
Patients will be instructed to return the ~~provisioned devices~~electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire~~ (visit 8)~~.	Patients will be instructed to return the electronic diary device on visit 5 and the electronic tablet on visit 8 to the investigational center after collection of the Special Protocol Headache Questionnaire.	Text updated to reflect collection of the electronic diary device and the electronic tablet will be at visit 5 and visit 8, respectively, as detailed in Letter of Clarification 06.
Section 7.1.7 Protocol-Defined Adverse Events of Special Interest		
Refer to ~~Appendix H~~ Appendix I for guidance regarding monitoring of patients with elevated liver function tests.	Refer to Appendix I for guidance regarding monitoring of patients with elevated liver function tests.	Correction to appendix hyperlinking.
Section 9.1 Sample Size and Power Considerations		
A sample size of 154 patients (77 evaluable patients per treatment group) ~~will~~was calculated to provide 80% power to detect a treatment difference of 2.0 days in the monthly average (assuming a common SD of 4.4 days) at a 2-sided alpha level of 0.05. Assuming a 10% discontinuation rate, 172 patients (86 patients per treatment group) ~~will~~were planned to be randomized in the study. Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.	A sample size of 154 patients (77 evaluable patients per treatment group) was calculated to provide 80% power to detect a treatment difference of 2.0 days in the monthly average (assuming a common SD of 4.4 days) at a 2-sided alpha level of 0.05. Assuming a 10% discontinuation rate, 172 patients (86 patients per treatment group) were planned to be randomized in the study. Study recruitment was discontinued at 87 patients due to challenges to enrollment and not for any safety concerns.	Clarification to the sample size as study enrollment was discontinued due to challenges to recruitment prior to reaching the target sample size.
Section 9.2.4 Per-Protocol Analysis Set		
The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any major protocol deviations ~~or unexpected drug concentration findings~~. Major protocol deviations will be determined before unblinding and database lock. ~~In the PP analysis set, treatment will be assigned based on the treatment patients actually received, regardless of the treatment to which they were randomized.~~	The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any major protocol deviations. Major protocol deviations will be determined before unblinding and database lock.	The definition of the per-protocol analysis set was modified as this is a subset of patients who completed the study as intended, only with a lack of major protocol deviations.
Section 9.5 Efficacy Analysis		

Original text with changes shown	New wording	Reason/Justification for change
The primary efficacy endpoint for this study will be derived from PTH data (presence of headache [yes/no]~~,~~ and peak severity [mild/moderate/severe]~~, and duration [<4 hours/4 hours]~~) collected daily using an electronic headache diary application.	The primary efficacy endpoint for this study will be derived from PTH data (presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.	Update to the primary efficacy analysis to coincide with the updated definition of a headache day in Section 2.1.1.
Section 9.5.5.1 Primary Efficacy Analysis		
The primary efficacy endpoint for this study will be derived from PTH data (ie, presence of headache [yes/no]~~,~~ and peak severity [mild/moderate/severe]~~, duration [<4 hours/4 hours], and prescription medication use [yes/no]~~) collected daily using an electronic headache diary application.	The primary efficacy endpoint for this study will be derived from PTH data (ie, presence of headache [yes/no] and peak severity [mild/moderate/severe]) collected daily using an electronic headache diary application.	Update to the primary efficacy analysis to coincide with the updated definition of a headache day in Section 2.1.1.
Section 10 Quality Control and Quality Assurance		
Refer to ~~Appendix C~~Appendix B 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 B 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.	Correction to appendix hyperlinking, as described in Letter of Clarification 09.
Section 11 Compliance Statement		
See ~~Appendix D~~Appendix C for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.	See Appendix C for the ethics expectations of informed consent or assent, competent authorities and IEC and IRB, confidentiality regarding study patients, and requirements for registration of the clinical study.	Correction to appendix hyperlinking, as described in Letter of Clarification 09.
Section 15 References		
See new changes column.	Finkel A, Yerry J, Klaric J, Ivins B, Scher A, Choi Y. Headache in military service members with a history of mild traumatic brain injury: a cohort study of diagnosis and classification. Cephalalgia 2017;37(6):548-59..	New reference cited in the introduction.
Section 16.2 Letter of Clarification 09 Dated 30 October 2019		

Original text with changes shown	New wording	Reason/Justification for change
This letter rectified the incorrect links (field codes) to some of the appendices and to update the sponsor's medical expert/contact in Appendix A.	This letter rectified the incorrect links (field codes) to some of the appendices and to update the sponsor's medical expert/contact in Appendix A.	This section was added to reflect the changes described in Letter of Clarification 09.
Section 16.3 Letter of Clarification 08 Dated 24 September 2019		
This letter clarified that the use of temperature loggers for the transport of pharmacokinetic samples was not needed in Appendix L (Pharmacokinetics Samples) as premium, next day couriers will be used and, thus, a temperature log will not be needed and the wording was removed.	This letter clarified that the use of temperature loggers for the transport of pharmacokinetic samples was not needed in Appendix L (Pharmacokinetics Samples) as premium, next day couriers will be used and, thus, a temperature log will not be needed and the wording was removed.	This section was added to reflect the changes described in Letter of Clarification 08.
16.4 Letter of Clarification 07 Dated 01 August 2019		
This letter clarified the total number of samples and the total volume of blood in Appendix G of the protocol. In Amendment 01, the number of samples (and the total volume) for clinical laboratory tests, pharmacokinetics, and biomarkers was revised. However, the number of samples and the associated blood volumes were not updated in Appendix G.	This letter clarified the total number of samples and the total volume of blood in Appendix G of the protocol. In Amendment 01, the number of samples (and the total volume) for clinical laboratory tests, pharmacokinetics, and biomarkers was revised. However, the number of samples and the associated blood volumes were not updated in Appendix G.	This section was added to reflect the changes described in Letter of Clarification 07.
16.5 Letter of Clarification 06 Dated 18 April 2019		
This letter clarified a typo in Appendix H, the Final Visit Day should read "168±3 days" instead of "16±3 days", the number of study centers was changed from 25 to 32 in Section 3.2 for consistency, footnote "v" in Table 1 was changed so that the provisioned electronic diary device should be returned at visit 5 to match footnote "m", and footnote "a" in Table 1 on the visit 1 column was put back in row 2 after being inadvertently omitted.	This letter clarified a typo in Appendix H, the Final Visit Day should read "168±3 days" instead of "16±3 days", the number of study centers was changed from 25 to 32 in Section 3.2 for consistency, footnote "v" in Table 1 was changed so that the provisioned electronic diary device should be returned at visit 5 to match footnote "m", and footnote "a" in Table 1 on the visit 1 column was put back in row 2 after being inadvertently omitted.	This section was added to reflect the changes described in Letter of Clarification 06.
Appendix A Clinical Laboratories and Other Departments and Institutions		

Original text with changes shown	New wording	Reason/Justification for change
Andrew Ahn, MD, PhD Vice President of Clinical Development, Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: ~~(610) 727-6128~~(610) 883-5503 Cell: (484) 983-9544	Andrew Ahn, MD, PhD Vice President of Clinical Development, Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: (610) 883-5503 Cell: (484) 983-9544	Update to sponsor contact information.
~~Jimmy Schiemann,~~ Juline Bryson, MD ~~Senior~~ Director Clinical Development, Migraine and Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: ~~610-727-6305~~610-786-7079 Fax: 610-786-7061 Cell: ~~484-502-6359~~484-401-2044	Juline Bryson, MD Director Clinical Development, Migraine and Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: 610-786-7079 Fax: 610-786-7061 Cell: 484-401-2044	Update to reflect the new sponsor medical expert.
~~Michael Burczynski~~Conrad Cowan Director, Translational Medicine ~~Personalized & Precision Medicine and Big Data Analytics~~ Teva Branded Pharmaceuticals R&D, Inc. Tel: ~~215-850-4392~~610-883-5843 Cell: ~~862-200-8781~~484-484-8259 Email: ~~Michael.Burczynski@tevapharm.com~~Conrad.Cowan01@tevapharm.com	Conrad Cowan Director, Translational Medicine Teva Branded Pharmaceuticals R&D, Inc. Tel: 610-883-5843 Cell: 484-484-8259 Email: Conrad.Cowan01@tevapharm.com	Update to reflect the new sponsor biomarker evaluator.
Appendix H Detailed Description of Assessments and Study Procedures		
Final Visit (End-of-Treatment/Early Termination/End-of-Study [Visit 8, Day ~~16~~168±3 days])	Final Visit (End-of-Treatment/Early Termination/End-of-Study [Visit 8, Day 168±3 days])	Correction to the study day number, as detailed in Letter of Clarification 06.
Appendix L Pharmacokinetics Samples (Other sections affected by this change: Appendix M)		
Set A samples will be transported ~~with a temperature data logger and~~ frozen with dry ice sufficient for 4 days, by next day courier to the central laboratory.	Set A samples will be transported frozen with dry ice sufficient for 4 days, by next day courier to the central laboratory.	The use of temperature data loggers are not needed as next day couriers are used.

Original text with changes shown	New wording	Reason/Justification for change
Appendix G Total Blood volume		
See new wording column.	Total Blood Volumes table has been modified as follows: • "Clinical laboratory tests and pregnancy" row: o Footnote "a" added o Total number of samples updated from 6 to 8 o Total volume (mL) updated from 36 to 48 • "FSH" row: o Footnote "b" added • "Pharmacokinetics" row: o Total number of samples updated from 5 to 7 o Total volume (mL) updated from 20 to 28 • "ADA" row: o Footnote "c" added • "Biomarkers" row: o Footnote "d" added o Total number of samples updated from 3 to 6 o Total volume (mL) updated from 55.5 to 111 • "Total" row: o Total number of samples updated from 19 to 26 o Total volume (mL) updated from 134.5 to 210 • Footnote "c" updated to coincide with the changes made to Table 1 footnote "o" • "AE=adverse event;" added to the table	Updates to the blood volumes as described in Letter of Clarification 07.

Original text with changes shown	New wording	Reason/Justification for change
	abbreviations.	

16.2. Letter of Clarification 09 Dated 30 October 2019

This letter rectified the incorrect links (field codes) to some of the appendices and to update the sponsor's medical expert/contact in Appendix A.

16.3. Letter of Clarification 08 Dated 24 September 2019

This letter clarified that the use of temperature loggers for the transport of pharmacokinetic samples was not needed in Appendix L (Pharmacokinetics Samples) as premium, next day couriers will be used and, thus, a temperature log will not be needed and the wording was removed.

16.4. Letter of Clarification 07 Dated 01 August 2019

This letter clarified the total number of samples and the total volume of blood in Appendix G of the protocol. In Amendment 01, the number of samples (and the total volume) for clinical laboratory tests, pharmacokinetics, and biomarkers was revised. However, the number of samples and the associated blood volumes were not updated in Appendix G.

16.5. Letter of Clarification 06 Dated 18 April 2019

This letter clarified a typo in Appendix H, the Final Visit Day should read "168±3 days" instead of "16±3 days", the number of study centers was changed from 25 to 32 in Section 3.2 for consistency, footnote "v" in Table 1 was changed so that the provisioned electronic diary device should be returned at visit 5 to match footnote "m", and footnote "a" in Table 1 on the visit 1 column was put back in row 2 after being inadvertently omitted.

16.6. Amendment 01 Dated 25 March 2019

The primary reason for this amendment is to incorporate the changes indicated from several administrative letters, to add language that specifies the estimand framework for the primary endpoint, and to specify key secondary endpoints. This amendment is considered to be substantial (ie, requires approval by CA, IEC, and/or IRB) by the sponsor's authorized representative. Other nonsubstantial changes have been made to the protocol (and protocol synopsis, as appropriate). 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 1 (Study Procedures and Assessments) and Figure 1 (Overall Study Schematic Diagram) have been revised to reflect changes described below.

Changes to the Protocol

Original text with changes shown	New wording	Reason/Justification for change
Clinical Study Protocol Synopsis		
Is this study conducted to investigate the New Use of an approved, marketed product? Yes~~No~~	**Is this study conducted to investigate the New Use of an approved, marketed product? Yes**	This change was made because the investigational product was approved in the United States after the previous version of the protocol was written.
Number of Investigational Centers Planned: This study is planned to be conducted in approximately ~~25~~32 investigational centers.	**Number of Investigational Centers Planned:** This study is planned to be conducted in approximately 32 investigational centers.	This change was made to increase the number of investigational centers planned in the study from 25 to 32.
Section 1.1 Introduction (Other sections affected by this change: Sections 2.1, 3.1, 3.3, 4.1, 4.2, 5.1.1, 5.3.1, 5.3.2, 6.1, 9.4, 9.5, 9.5.5)		
~~PPTH~~PTH	PTH	This change was made to remove "persistent" from "persistent posttraumatic headache" throughout the protocol to expand eligibility.
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Sections 2.1.1, 2.2, 3.1, 3.5, 4.1, 5.8, 6.1, 6.5, 9.5.1, 9.5.2, 9.5.4, Appendix H)		
The **primary efficacy endpoint** is the mean change from baseline (~~run in~~ baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.	The **primary efficacy endpoint** is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of the IMP.	The term "run-in" period was changed to "baseline" period throughout the protocol due to team preference in terminology. Baseline was determined to be more appropriate.
Section 2.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Sections 3.1, 3.5, 5.1.1.1, 9.9, Appendix H)		
A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered sc in adult patients with ~~P~~PTH compared with placebo and during the open-label period.	A **secondary objective** of the study is to evaluate the safety and tolerability of fremanezumab administered sc in adult patients with PTH compared with placebo and during the open-label period.	This change was made because an open-label period was added to this study.
Section 2.1.1 Primary and Secondary Study Objectives and Endpoints (Other sections affected by this change: Sections 4.1, 5.8)		
A headache day is defined as a day when a patient reports at least 4 hours of headache (not necessarily consecutive) and at its worst at any point has at least moderate severity; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity).	A headache day is defined as a day when a patient reports at least 4 hours of headache (not necessarily consecutive) and at its worst at any point has at least moderate severity; or when a patient has a headache and takes a prescription abortive medication with intent to alleviate the headache (regardless of duration or severity).	The term "abortive" was added to specify the type of prescription medication taken by patients to alleviate headache.

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

Original text with changes shown	New wording	Reason/Justification for change
[redacted]	[redacted]	[redacted]
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]
Section 3.1 General Study Design and Study Schematic Diagram		
The study will consist of a screening visit, a ~~run-in~~ baseline period, ~~and~~ a double-blind treatment period lasting approximately 12 weeks, and an open-label period lasting approximately 12 weeks. ~~Follow-up visits will take place approximately 24 weeks (phone visit) and approximately 40 weeks after the first dose of the IMP.~~	The study will consist of a screening visit, a baseline period, a double-blind treatment period lasting approximately 12 weeks, and an open-label period lasting approximately 12 weeks.	This change was made to include the open-label period of approximately 12 weeks and to remove all follow-up visits from the study.
The total duration of patient participation in the study is planned to be approximately ~~44~~28 weeks.	The total duration of patient participation in the study is planned to be approximately 28 weeks.	This change was made to adjust the study duration from 44 weeks to 28 weeks to reflect the new study schedule and the addition of an open-label period. .
Patients will complete a screening visit (visit 1) after providing informed consent, and eligible patients will enter a ~~run-in~~baseline period lasting approximately 4 weeks (28+3 days), during which time they will enter their baseline PTH information into ~~an~~a daily electronic headache diary ~~application daily. The diagnosis will be prospectively confirmed via a review of headache data recorded daily during a 28-day run-in period in an electronic headache diary device.~~	Patients will complete a screening visit (visit 1) after providing informed consent, and eligible patients will enter a baseline period lasting approximately 4 weeks (28+3 days), during which time they will enter their baseline PTH information into a daily electronic headache diary.	Information was removed regarding confirmation of the diagnosis from the e-diary review.
Patients meeting eligibility requirements will be randomly assigned to 1 of 2 treatment groups with fremanezumab or	Patients meeting eligibility requirements will be randomly assigned to 1 of 2 treatment groups	These changes were made to specify the 2 possible treatment groups in the study:

Original text with changes shown	New wording	Reason/Justification for change
placebo in a 1:1 ratio. Treatment assignment will take place with stratification based on the duration of the patient's history of posttraumatic headache ~~onset~~ (<12 months and ≥12 months ~~since the brain injury) to 1 of 2 treatment groups with fremanezumab or placebo in a 1:1 ratio.~~duration).	with fremanezumab or placebo in a 1:1 ratio. Treatment assignment will take place with stratification based on the duration of the patient's history of posttraumatic headache (<12 months and ≥12 months duration).	fremanezumab and placebo. Changes were also made to specify that patients will be randomly assigned in a 1:1 ratio. Specifications for duration of the patient's history of posttraumatic headache were generalized for clarification.
~~Baseline procedures and~~Screening results will be reviewed for eligibility, additional baseline assessments will be administered, and the first treatment administration will occur at visit 2.	Screening results will be reviewed for eligibility, additional baseline assessments will be administered, and the first treatment administration will occur at visit 2.	This change was made to replace baseline procedures with screening results.
Patients will return to the study center approximately every 4 weeks (visit 3 and visit 4) for a continuation of the blinded treatment administered sc; for safety and efficacy assessments; and for blood and urine sampling for pharmacokinetics, immunogenicity, ~~biomarkers~~, and ~~pharmacogenomics (unless prohibited by local regulations) analyses~~.biomarker analysis.	Patients will return to the study center approximately every 4 weeks (visit 3 and visit 4) for a continuation of the blinded treatment administered sc; for safety and efficacy assessments; and for blood and urine sampling for pharmacokinetics, immunogenicity, and biomarker analysis.	This change was made to clarify that patients will return to the study center during an open-label period of the study. Pharmacogenomics was removed from the study endpoints.
At visit 5, all patients will proceed directly to an open-label treatment phase, with fremanezumab administered sc. Patients will then return to the study center approximately every 4 weeks (visits 6, and 7) for continued open-label treatment and safety tolerability and efficacy assessments. Final study assessments will be performed on visit 8, at the end of treatment or early termination visit~~ (visit 5)~~, approximately ~~12~~24 weeks after first administration of the IMP.	At visit 5, all patients will proceed directly to an open-label treatment phase, with fremanezumab administered sc. Patients will then return to the study center approximately every 4 weeks (visits 6 and 7) for continued open-label treatment and safety tolerability and efficacy assessments. Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP.	Visit 5 was changed to the first visit of the open-label period. Visits 6, 7, and 8 were added to the open-label period, with approximately 4 weeks between visits. Visits 6 and 7 were added as dosing visits, and Visit 8 is the EOS visit.
~~Following~~For all patients in the study, the end-of -treatment visit (visit ~~5),~~8) is defined as the final visit of the study and the conclusion of all study activities for the patient; patients will not receive any further treatments with IMP and ~~should~~will be treated according to guidelines and treating physicians' discretion.	For all patients in the study, the end-of-treatment visit (visit 8) is defined as the final visit of the study and the conclusion of all study activities for the patient; patients will not receive any further treatments with IMP and will be treated according to guidelines and treating physicians' discretion.	This change was made to define the end-of-treatment visit.
~~Patients will be contacted by telephone for a follow-up visit (visit 6) approximately 24 weeks after the first dose of IMP to have efficacy procedures completed and will report to the investigational center for a final follow-up visit (visit 7)~~	However, a final database lock will occur following the end-of-treatment visit (visit 8) of the last patient for analysis of the study data.	The telephone visit was removed from this study. The final follow-up visit was changed to visit 8 to account for the addition of visits 6 and 7 in the open-label

Original text with changes shown	New wording	Reason/Justification for change
~~approximately 40 weeks following the first dose of IMP to have final procedures and assessments performed. The end of study is defined as the last follow-up visit.~~ However, a final~~an interim~~ database lock will occur following the end-of-treatment visit (visit ~~5~~8) of the last patient for analysis of the study data.		period. This change supersedes the alterations requested in the letter of clarification dated 01 October 2018.
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Section 3.2)		
The total duration of the study will be approximately 2 years from Q4 of 2017 until approximately ~~Q4~~Q2 of ~~2019~~2020.	The total duration of the study will be approximately 2 years from Q4 of 2017 until approximately Q2 of 2020.	This change was made to extend the total duration of the study from Q4 2019 to Q2 2020.
Section 3.1 General Study Design and Study Schematic Diagram (Other sections affected by this change: Section 9.14)		
Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP. A database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.	Final study assessments will be performed on visit 8, at the end of treatment or early termination visit, approximately 24 weeks after first administration of the IMP. A database lock from the double-blind period will occur following the completion of visit 5 by the last patient. Unblinding will occur after the database lock from the double-blind period.	This change was made to clearly state the intent to analyze data following the completion of visit 5 by the last patient.
Section 3.3 Justification for Study Design and Selection of Population (Other sections affected by this change: Sections 4.1, 4.5, 9.5)		
~~PPTH~~PTH is a headache with >~~3 months~~1 month duration	PTH is a headache with >1 month duration	This change was made to reduce the length of headache duration from 3 months to 1 month.
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 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, protocol deviation as defined in Section 10, noncompliance, or adverse event).	This change was made to remove the term "protocol violation" language from the protocol. Protocol deviation is the preferred language.
Section 4. 1 Patient Inclusion Criteria		
In addition, the following criteria should be met: Headache persists for >~~3 months~~ 1 month after injury to the head ~~And/or~~ ~~Whiplash has occurred and is associated at the time with neck pain and/or headache~~ ~~Headache has developed within 7 days after the whiplash~~ ~~Headache persists for >3 months after the whiplash~~	In addition, the following criteria should be met: Headache persists for >1 month after injury to the head	This criterion was modified to expand patient eligibility by lowering the symptom timeframe. Also, whiplash as a headache etiology was removed to clarify the indication.

Original text with changes shown	New wording	Reason/Justification for change
Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening and a negative urine pregnancy test at baseline, are sterile, or postmenopausal. Definitions of sterile and postmenopausal are given in Appendix D.	Women may be included only if they have a negative serum beta-human chorionic gonadotropin (β-HCG) test at screening and a negative urine pregnancy test at baseline, are sterile, or postmenopausal. Definitions of sterile and postmenopausal are given in Appendix D.	This text was added to clarify that Appendix D further elaborates on definitions of sterile and postmenopausal.
Men must be sterile or, if they are potentially fertile or reproductively competent (ie, not surgically or congenitally sterile), must use, together with their female partners, a condom for the duration of the study and for 30 weeks after the last IMP administration. Further details are included in Appendix D.	Men must be sterile or, if they are potentially fertile or reproductively competent (ie, not surgically or congenitally sterile) and their female partners are of childbearing potential, must use, together with their female partners, a condom for the duration of the study and for 30 weeks after the last IMP administration. Further details are included in Appendix D.	This text was added to clarify that men in the study, or men with female partners who are participating in the study, must use a condom as a birth control method.
Definitions of WOCBP, sterile and postmenopausal women, male contraception, and highly effective ~~and acceptable~~ birth control methods, including examples, are given in Appendix D.	Definitions of WOCBP, sterile and postmenopausal women, male contraception, and highly effective birth control methods, including examples, are given in Appendix D.	This change was made to remove acceptable birth control from the protocol. Only effective birth control will be used.
Section 4. 2 Patient Exclusion Criteria		
The patient has a previous history of brain imaging showing evidence of intracerebral hemorrhage, subdural or epidural hematomas, or subarachnoid hemorrhage as a consequence of the traumatic head injury. Brain images with structurally insignificant changes, as discussed and approved by the sponsor, will be reviewed by the sponsor on a case-by-case basis.	The patient has a previous history of brain imaging showing evidence of intracerebral hemorrhage, subdural or epidural hematomas, or subarachnoid hemorrhage as a consequence of the traumatic head injury. Brain images with structurally insignificant changes, as discussed and approved by the sponsor, will be reviewed by the sponsor on a case-by-case basis.	This change was made to include patients who have brain images with structurally insignificant changes, if agreed upon by the sponsor. This will allow for more potential study participants.
The patient has whiplash ~~with only neck pain~~ and ~~no persistent~~subsequent headache ~~>3 months after whiplash~~but no history of head injury or concussion.	The patient has whiplash and subsequent headache but no history of head injury or concussion.	This change was made to add subsequent headache to this exclusion criterion, following whiplash.
The patient has participated in another study of an IMP (or a medical device) within the previous 30 days (or 90 days for biologics) or 5.5 half-lives, whichever is longer, of the IMP or is currently participating in another study of an IMP (or a medical device) prior to screening.	The patient has participated in another study of an IMP (or a medical device) within the previous 30 days (or 90 days for biologics) or 5.5 half-lives, whichever is longer, of the IMP or is currently participating in another study of an IMP (or a medical device) prior to screening.	This change was made to specify that this exclusion criterion refers to the time period before screening in this study.
The patient has had exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab, galcanezumab and	The patient has had exposure to a mAb targeting the CGRP pathway (erenumab, eptinezumab,	This exclusion criterion was added to specify that patients with exposure to a

Original text with changes shown	New wording	Reason/Justification for change
fremanezumab) during the 6 months prior to the day of the screening visit.	galcanezumab, and fremanezumab) during the 6 months prior to the day of the screening visit.	mAb targeting the CGRP pathway during the 6 months prior to the study will not be included.
The patient is not currently ~~using or has prior exposure to any CGRP antibody, any antibody to the CGRP receptor. The patient has received~~ being treated with onabotulinmumtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the ~~previous~~ 3 months ~~before~~prior to the screening visit.	The patient is not currently being treated with onabotulinmumtoxinA (eg, Botox, Dysport, Xeomin) application in the head or neck or has received any such injection during the previous 3 months prior to the screening visit.	These changes were made to clarify that patients should not be treated (currently or during the 3 months prior to screening) with onabotulinmumtoxinA application. Xeomin was added to the list of such applications.
The patient has been implanted with any electronic devices for headache ~~prophylaxis~~ prevention during the ~~previous~~ 3 months ~~before screening~~prior to the screening visit or is currently using any implanted or externally applied stimulator or device.	The patient has been implanted with any electronic devices for headache prevention during the 3 months prior to the screening visit or is currently using any implanted or externally applied stimulator or device.	These changes were made to specify that electronic devices implanted for headache are not permitted in this study.
The patient has major depression as assessed by the 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9) at screening. Any patient with a score ≥15 should be considered to have major depression and should be referred for appropriate treatment. Patients with lower scores (5 to 14) may also have major depression, and they should be carefully evaluated by the investigator for the presence of additional symptoms.	The patient has major depression as assessed by the 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9) at screening. Any patient with a score ≥15 should be considered to have major depression and should be referred for appropriate treatment. Patients with lower scores (5 to 14) may also have major depression, and they should be carefully evaluated by the investigator for the presence of additional symptoms.	This text was added to further elaborate on the PHQ scores to describe which scores indicate that patients may have major depression.
The patient has a history of alcohol abuse or recreational drug abuse or at the discretion of the investigator is suspected of abusing alcohol or recreational drugs.	The patient has a history of alcohol abuse or recreational drug abuse or at the discretion of the investigator is suspected of abusing alcohol or recreational drugs.	This text was added to include the ability of the investigator to suspect alcohol or recreational drug abuse in patients to exclude them from the study.
The patient has ~~exhibited~~any lifetime history of suicidal behaviors (~~actual~~suicide attempts, interrupted attempts, aborted attempts~~, and preparatory actions~~suicidal ideation, or preparations for suicide).	The patient has any lifetime history of suicidal behaviors (suicide attempts, interrupted attempts, aborted attempts, suicidal ideation, or preparations for suicide).	These changes were made to clarify suicidal behavior.
Section 4. 3 Withdrawal Criteria and Procedures for the Patient		
Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care	Each patient is free to withdraw from the study or discontinue from IMP at any time, without prejudice to their continued care	This text was added to specify that patients may discontinue from the IMP at any time.

Original text with changes shown	New wording	Reason/Justification for change
Investigators should attempt to obtain information on patients in the case of withdrawal from the study or discontinuation from IMP.	Investigators should attempt to obtain information on patients in the case of withdrawal from the study or discontinuation from IMP.	These changes were made to clarify that patients may withdraw from the study or discontinue from IMP.
Section 4.5 Rescreening		
Patients who historically screen-failed or have currently failed screening as a result of the following previous criteria will be rescreened if both conditions apply: • headache persists for >1 month after injury to the head • e-diary compliance level of 75%. A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again unless approved by the sponsor on a case-by-case basis. Patients enrolled after rescreening will be given a new patient identification number.	Patients who historically screen-failed or have currently failed screening as a result of the following previous criteria will be rescreened if both conditions apply: • headache persists for >1 month after injury to the head • e-diary compliance level of 75% A patient who is screened and does not meet study inclusion and exclusion criteria will not be considered for screening again unless approved by the sponsor on a case-by-case basis. Patients enrolled after rescreening will be given a new patient identification number.	Due to changes in the eligibility criteria, this change was made to include sponsor approval of rescreening on a case-by-case basis and to clarify the criteria for rescreening.
Section 5.1.1.1 Starting Dose and Dose Levels (Other sections affected by this change: Section 3.5)		
Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 2 (~~week 0) , visit 3 (week 4), and visit 4 (week 8).~~randomization), visit 3 (week 4), and visit 4 (week 8). Patients will then enter the open-label period of the study, where they will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20).	Patients randomized to fremanezumab will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 2 (randomization), visit 3 (week 4), and visit 4 (week 8). Patients will then enter the open-label period of the study, where they will receive 675 mg of fremanezumab administered as 3 sc injections (225 mg/1.5 mL each) at visit 5 (week 12), visit 6 (week 16), and visit 7 (week 20).	These changes were made to include the injection schedules and doses for both the blinded period and the open-label period.
Section 5.4 Treatment After the End of the Study		
~~A telephone visit will take place approximately 24 weeks following administration of the first dose of IMP to assess efficacy.~~	Deleted text	The follow-up telephone visit was removed from the study. There will be no follow-up visit in the adjusted study.
Section 5.6 Prior and Concomitant Medication or Therapy		
For daily-prescribed medications and preventative treatments, patients must be on a stable dose and regimen for at least 2 weeks prior to screening and maintained throughout the study until the completion of visit ~~5~~8.	For daily-prescribed medications and preventative treatments, patients must be on a stable dose and regimen for at least 2 weeks prior to screening and maintained throughout the study until the completion of visit 8.	This change was made to include the allowance of preventative treatments concomitantly with the dosing regimen.

Original text with changes shown	New wording	Reason/Justification for change
Section 5.8 Randomization and Blinding (Other sections affected by this change: Section 4.1, 4.5, and 6.1)		
Electronic diary ~~card~~ completion must be at least ~~85~~75% during the ~~run in~~baseline period for randomization eligibility and at least 75% during the double-blind treatment period, during which the patient cannot miss more than 7 days of recording nor more than 4 days in a row.	Electronic diary completion must be at least 75% during the baseline period for randomization eligibility and at least 75% during the double-blind treatment period, during which the patient cannot miss more than 7 days of recording nor more than 4 days in a row.	These changes were made to adjust the electric diary completion percentage from 85% to 75%.
Section 5.9.1 Maintenance of Randomization		
~~At the time of analysis~~After all patients have completed visit 5~~(after the end of the study), after receiving~~ and an unblinding request from the Teva statistician has been received, the third-party vendor will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure.	After all patients have completed visit 5 and an unblinding request from the Teva statistician has been received, the third-party vendor will provide the unblinded IMP assignments according to the processes defined in the relevant Standard Operating Procedure.	These changes were made to clarify that unblinding will occur after all patients have completed visit 5.
Section 5.9.2 Blinding and Unblinding		
the investigator may unblind the patient's IMP assignment before the open-enrollment period as deemed necessary	the investigator may unblind the patient's IMP assignment before the open-enrollment period as deemed necessary	This text has been added to clarify that the IMP assignment may be unblinded before the open-enrollment period.
Section 6.5 Special Protocol Headache Questionnaire		
~~Patients will then be contacted by telephone for a follow-up visit (visit 6) approximately 12 weeks following the last study visit (visit 5) and will be asked if they had any headaches since the last study visit. For those who experienced headache(s), an additional 12 questions will be asked regarding the number, severity, frequency, and duration of the headache(s) and their effect on daily activities and sleep.~~Patients will be instructed to return the provisioned devices to the investigational center after collection of the Special Protocol Headache Questionnaire (visit 8).	Patients will be instructed to return the provisioned devices to the investigational center after collection of the Special Protocol Headache Questionnaire (visit 8).	This text was modified to clarify the instructions on returning devices to the investigational center. End of study was changed from visit 6 to visit 8 to reflect the addition of the open-label period. All text relating to the follow-up telephone visit has been removed from the protocol. There will no longer be a telephone follow-up visit.
Section 9.2.4 Per-Protocol Analysis Set		
The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any major protocol ~~deviations~~deviations or ~~who have~~ unexpected drug concentration findings.	The per-protocol (PP) analysis set is a subset of the ITT analysis set including only patients without any major protocol deviations or unexpected drug concentration findings.	This change was made to clarify which patients are included in the per-protocol analysis set.
Section 9.5.5.1 Primary Efficacy Analysis		
The primary estimand for this study is defined by the following attributes:	The primary estimand for this study is defined by the following attributes:	This change was made as part of a recommendation to include the estimand framework.

Original text with changes shown	New wording	Reason/Justification for change
• The target population includes male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by the ICHD-3 [beta version] criteria). • The primary outcome measure is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP. • The FAS will be used for efficacy analyses. FAS is a subset of the ITT analysis set and includes only patients who receive at least 1 dose of IMP and have at least 1 postbaseline efficacy assessment on the primary endpoint. In the FAS, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. • Treatment effect will be measured via ANCOVA method, including treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariates. For patients assigned to active treatment who discontinue the study due to lack of efficacy, death, or adverse event, the proportion of headache days in the remainder of the analysis window will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to placebo. All other missing data for patients in either treatment group will be handled as follows: • For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number	• The target population includes male and female patients aged 18 to 70 years, inclusive, with a history of PTH (as defined by the ICHD-3 [beta version] criteria). • The primary outcome measure is the mean change from baseline (baseline period) in the monthly average number of headache days of at least moderate severity during the 12-week period after the first dose of IMP. • The FAS will be used for efficacy analyses. FAS is a subset of the ITT analysis set and includes only patients who receive at least 1 dose of IMP and have at least 1 postbaseline efficacy assessment on the primary endpoint. In the FAS, treatment will be assigned based on the treatment to which patients were randomized, regardless of which treatment they actually received. • Treatment effect will be measured via ANCOVA method, including treatment as fixed effect and the baseline number of headache days of at least moderate severity and the PTH onset (<12 months and ≥12 months) as covariates. For patients assigned to active treatment who	

Original text with changes shown	New wording	Reason/Justification for change
<u>of headache days will be calculated based on data available in that analysis window and prorated to 28 days.</u> • For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data. Sensitivity analyses will be conducted as defined in the statistical analysis plan.	discontinue the study due to lack of efficacy, death, or adverse event, the proportion of headache days in the remainder of the analysis window will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to placebo. All other missing data for patients in either treatment group will be handled as follows: • For patients who have ≥10 days of e-diary data in an analysis window, the monthly average number of headache days will be calculated based on data available in that analysis window and prorated to 28 days. • For patients who have <10 days of e-diary data in an analysis window, the monthly average number of headache days will be imputed as the mean monthly average of headache days in the same analysis window for patients assigned to the same treatment group and having ≥10 days of e-diary data. Sensitivity analyses will be conducted as defined in the statistical analysis plan.	

Original text with changes shown	New wording	Reason/Justification for change
Section 9.5.5.2 Sensitivity Analysis		
Sensitivity analysis ~~may be performed~~will be conducted to explore the impact of missing data in the primary efficacy analysis. In particular, endpoints analyzed using an ANCOVA method will be analyzed using a mixed model for repeated measures method. The details will be described in the statistical analysis plan.	Sensitivity analysis will be conducted to explore the impact of missing data in the primary efficacy analysis. In particular, endpoints analyzed using an ANCOVA method will be analyzed using a mixed model for repeated measures method. The details will be described in the statistical analysis plan.	This change was made as part of a recommendation to include the estimand framework.
Section 9.5.5.3 Secondary Efficacy Analysis		
For the proportion of responders defined as 50% or more reduction from baseline in the monthly average headache days, the Cochran-Mantel-Haenszel test will be used stratified by PTH onset (<12 months and ≥12 months).	For the proportion of responders defined as 50% or more reduction from baseline in the monthly average headache days, the Cochran-Mantel-Haenszel test will be used stratified by PTH onset (<12 months and ≥12 months).	This change was made as part of a recommendation to include the estimand framework.
Section 9.6 Multiple Comparisons and Multiplicity		
Testing of statistical significance at a 2-sided alpha of 0.05 will be performed for the primary endpoint. If the primary endpoint meets statistical significance, then each of the key secondary endpoints will be tested for significance in a pre-specified order at a 2-sided alpha of 0.05. If and when any p>0.05, no further comparisons will be interpreted inferentially. Details will be presented in the statistical analysis plan.	Testing of statistical significance at a 2-sided alpha of 0.05 will be performed for the primary endpoint. If the primary endpoint meets statistical significance, then each of the key secondary endpoints will be tested for significance in a pre-specified order at a 2-sided alpha of 0.05. If and when any p>0.05, no further comparisons will be interpreted inferentially. Details will be presented in the statistical analysis plan.	This change was made as part of a recommendation to include the estimand framework.
Section 9.9 Pharmacokinetic Analysis		
Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point. At the open-label period, pharmacokinetic plasma concentration results will be tabulated descriptively at each planned sampling time point treatment group.	Pharmacokinetic plasma concentration results for fremanezumab will be tabulated descriptively at each planned sampling time point. At the open-label period, pharmacokinetic plasma concentration results will be tabulated descriptively at each planned sampling time point treatment group.	This text was added to clarify that pharmacokinetic plasma concentration results will be tabulated descriptively at sampling time points.

16.7. Letter of Clarification 05 Dated 01 October 2018

This letter clarified the requirements for the telephone call in Section 6.5. However, this paragraph was removed during review of the amendment due to the removal of the phone call.

16.8. Letter of Clarification 04 Dated 06 February 2018

This letter clarified the requirements for the exclusion criterion related to major depression; at what PHQ-2/PHQ-9 score a patient would be excluded.

16.9. Letter of Clarification 03 Dated 11 December 2017

This letter specified in inclusion criterion ‘f’ which prescription medications support the determination of moderate severity. However, this criterion was further modified during review of the amendment.

16.10. Letter of Clarification 02 Dated 16 November 2017

This letter clarified the requirements for prior or concomitant medication or therapies in Section 5.6 and Appendix F.

16.11. Letter of Clarification 01 Dated 10 November 2017

This letter clarified the use of the word “capsule” in the model ICF.

APPENDIX A. CLINICAL LABORATORIES AND OTHER DEPARTMENTS AND INSTITUTIONS

Sponsor's Authorized Representative	Andrew Ahn, MD, PhD Vice President of Clinical Development, Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: (610) 883-5503 Cell: (484) 983-9544
Sponsor's Medical Expert/Contact Point Designated by the Sponsor for Further Information on the Study	Juline Bryson, MD Director Clinical Development, Migraine and Headache Teva Branded Pharmaceutical Products R&D, Inc. Tel: 610-786-7079 Fax: 610-786-7061 Cell: 484-401-2044
Sponsor's Contact Point Designated by the Sponsor for Further Information on the Study	Sarah Swanson Sr Manager, Global Clinical Project Management Global Clinical Operations, CNS & Pain Teva Branded Pharmaceutical Products R&D, Inc. Tel: 610-893-1074 Fax: 610-786-7061 Cell: 484-319-5807
Study Coordinating Investigators	Egilius L.H. Spierings, MD, PhD Medical Director and Principal Investigator, MedVadis Research Corporation Watertown, MA 02472 Tel: 617-777-1310 Fax: 617-744-1285 Cell: 781-588-5430 Stephen Silberstein, MD Director, Jefferson Headache Center, Dept. of Neurology 900 Walnut Street, 2nd floor, Suite #200 Philadelphia, PA 19107 Tel: 215-955-2727 Cell: 215-955-2243

Sponsor's Representative of Global Patient Safety and Pharmacovigilance For **serious adverse events:** Send by email to the local safety officer/contract research organization (LSO/CRO). 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.	Yoel Kessler, MD, MBA Safety Physician Director Global Patient Safety & Pharmacovigilance Tel: +972 9 836 1265 Cell: + 972 54 944 5889
Contract Research Organization	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Central Clinical Laboratory	ICON Clinical Research Services 123 Smith Street Farmingdale, NY 11735 United States
Central Electrocardiogram Evaluation	Spaulding Clinical Research, LLC 525 S. Silverbrook Dr. West Bend, Wisconsin 53095
Bioanalytical Pharmacokinetics and Immunogenicity Evaluation	Michele Rasamoelisolo, PhD Director PK/PD Bioanalytics, Global Bioassays and Technology Teva Branded Pharmaceuticals R&D, Inc. Tel: 610-738-6111 Email: Michele.Rasamoelisolo@tevapharm.com Orit Cohen-Barak, PhD (pharmacokinetics evaluation) Associate Director Clinical Pharmacology Teva Branded Pharmaceuticals R&D, Inc. Tel: 972-9-892-1799 Email: Orit.Cohen-Barak@teva.co.il
Biomarker Evaluation	Conrad Cowan Director, Translational Medicine Teva Branded Pharmaceuticals R&D, Inc. Tel: 610-883-5843 Cell: 484-484-8259 Email: Conrad.Cowan01@tevapharm.com
Electronic Clinical Outcome Assessment	Medidata Solutions Worldwide 350 Hudson Street New York, NY 10014
eC-SSRS Scale	eResearch Technology, Inc 1818 Market Street #1000 Philadelphia, PA, 19103

Web and Phone Integrated Interactive Response Technology	Medidata Solutions Worldwide 350 Hudson Street New York, NY 10014

APPENDIX B. 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 (IEC)/Institutional Review Board (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.

Important 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 a major protocol deviation. Major 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 recorded by the contract research organization in the appropriate system defined in the clinical management plan. All protocol deviations will be reported to the responsible IEC/IRB, as required.

When a major 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 or designee. The decision will be based on ensuring the safety of the patient and preserving the integrity of the study.

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. 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 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 C. 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 (IEC)/Institutional Review Board (IRB). All written and oral information about the study will be provided in a language as nontechnical as practical to be understood by the patient. The patient should be given ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. The above should be detailed in the source documents.

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

Competent Authorities and Independent Ethics Committees/Institutional Review Boards

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

Confidentiality Regarding Study Patients

The investigator must ensure that the privacy of the patients, including their identity and all personal medical information, will be maintained at all times. In 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 D. BIRTH CONTROL METHODS AND PREGNANCY TESTING

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

Drug interaction studies have not been conducted with fremanezumab. Like other therapeutic antibodies, fremanezumab is expected to be metabolized primarily via proteolytic catabolism. Therefore, interaction with and impact on drug metabolizing enzymes (eg, cytochrome P-450 [CYP] isoforms) is considered unlikely in humans.

In addition, fremanezumab is not expected to indirectly influence 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 pro-inflammatory cytokine release in human whole blood (Study 111320). Fremanezumab did no elicit significant cytokine release (tumor necrosis factor alpha, interleukin [IL]-6, interferon gamma, 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/Girls of childbearing potential are defined as:

- not surgically (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or congenitally sterile
- not postmenopausal

Postmenopausal women:

- 1 year postmenopausal (no menses for 12 months without an alternative medical cause plus an increased concentration of FSH of more than 35 U/L) in women not using hormonal contraception or hormonal replacement therapy

Description of different birth control methods

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 1 cycle (for IMPs without suspected teratogenicity/genotoxicity) before the first dose of IMP.

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation; these should be initiated at least 1 cycle (for IMPs without suspected teratogenicity/genotoxicity) before the first dose 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 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).

Unacceptable birth control methods:

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

Male contraception:

Male patients must always use a condom.

Vasectomy:

Use of contraceptive methods also applies to vasectomized men because of the risk associated with transfer of a drug via seminal fluid.

Contraception for female partners of male study participants:

Male study participants must use a condom if their female partners are of childbearing potential until the end of relevant systemic exposure.

Pregnant female partners of male study participants:

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

APPENDIX E. LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.

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

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

APPENDIX F. LIST OF PROHIBITED MEDICATIONS AND PROCEDURES AND ALLOWED MEDICATIONS WITH SPECIAL CONDITIONS

Prohibited Medications and Procedures

The following medications will be prohibited during this study:

- analgesic medications containing opioids (including codeine) if used for more than 15 days per month
- a barbiturate if used for more than 15 days per month
- calcitonin gene-related peptide (CGRP) antibody or any antibody to the CGRP receptor
- OnabotulinumtoxinA (eg, Botox, Dysport, Xeomin)
- devices for headache prophylaxis
- nerve block for head and/or neck

All patients will be questioned about concomitant medications at each study visit.

Allowed Medications with Special Conditions

Patients will be allowed to take the following medications during the study only if they were started at least 2 months before screening. In that case, the dose regimen should be maintained with no modifications until visit 8. These medications should not be started before visit 8.

- atenolol, propranolol, metoprolol, nadolol, timolol, flunarizine, pizotifen, amitriptyline, venlafaxine, nortriptyline, duloxetine, topiramate, valproate, carbamazepine, fivalproate, candesartan, and lisinopril

APPENDIX G. TOTAL BLOOD VOLUME

The total blood volume to be collected for each patient in this study is approximately 210 mL.

Total Blood Volumes

Type of samples	Volume per sample (mL)	Total number of samples	Total volume (mL)
Clinical laboratory tests and pregnancy[a]	6	8	48
FSH[b]	3	1	3
Pharmacokinetics	4	7	28
ADA[c]	5	4	20
Biomarkers[d]	18.5	6	111
Total	--	**26**	**210**

[a] A serum pregnancy test will be performed for women of childbearing potential only.
[b] Postmenopausal women only.
[c] A blood sample for ADA assessment will be collected prior to dosing at each applicable visit and will also be collected upon observation of severe hypersensitivity or anaphylaxis or if there is a suspected causal relationship of an AE potentially being related to immunogenicity (eg, lack of efficacy).
[d] Each 18.5 mL sample will be divided into 3 samples: 6 mL each for serum and plasma and 6.5 mL for RNA.
ADA=anti-drug antibody; AE=adverse event; FSH=follicle-stimulating hormone.

APPENDIX H. DETAILED DESCRIPTION OF ASSESSMENTS AND PROCEDURES

1. **Procedures for Screening (Visit 1, Day -28 to -1 [+3 days])**

The screening visit (visit 1) will take place 28 days before the randomization visit (visit 2). The following procedures will be performed at visit 1:

- Obtain written informed consent before any study-related procedures are performed.
- Review inclusion and exclusion criteria.
- Obtain medical and psychiatric history.
- Obtain prior medication and treatment history.
- Record demographic characteristics.
- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform a full physical examination (including height and weight).
- Perform 12-lead electrocardiogram (ECG) in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform beta-human chorionic gonadotropin (β-HCG) serum pregnancy test (for women of childbearing potential).
- Perform serum FSH test (for postmenopausal women).
- Inform patients of study restrictions and compliance requirements.
- Complete electronic headache diary. (Note: This will be completed by the patient daily at home during the baseline period.)
- Complete the 2-item Patient Health Questionnaire (PHQ-2)/9-item Patient Health Questionnaire (PHQ-9).
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) Baseline/Screening version.
- Inquire about adverse events
- Inquire about concomitant medications.

1. **Procedures Before Administration of Investigational Medicinal Product (Baseline [Visit 2, Day 0±3 days])**

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

The following procedures will be performed predose at visit 2:

- Review inclusion and exclusion criteria.
- Assign randomization/treatment number.
- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform a full physical examination (including weight).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a urine pregnancy test for women of childbearing potential.
- Review study compliance.
- Complete and review electronic headache diary.
- Obtain a 4 mL blood sample for plasma concentration of investigational medicinal product (IMP).
- Obtain a 5 mL blood sample for serum anti-drug antibodies (ADAs) assay.
- Obtain an 18.5 mL blood sample and a urine sample for biomarkers analysis.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the 6-item Headache Impact Test (HIT-6) questionnaire.
- Complete the 12-item Short-Form Health Survey (SF-12) questionnaire.
- Complete the Sport Concussion Assessment Tool 3rd edition (SCAT-3) questionnaire.
- Complete the Patient Global Impression of Change (PGIC) questionnaire.
- Complete the C-SSRS Since Last Visit version.
- Inquire about concomitant medications.

Patients who meet eligibility criteria will be randomized to 1 of 3 treatment groups.

2. **Procedures During Administration of Investigational Medicinal Product (Double-Blind Treatment Period [Visits 2 through 4, Days 0 through 84±3 days])**

Eligible patients will complete entries of posttraumatic headache information (presence, severity, and duration) daily from visit 2 through visit 5. See Section 6.1 of the protocol for additional details.

Visit 2 (Day 0±3 days)

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

- Administer IMP.

- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.
- Evaluate for anaphylaxis or hypersensitivity reaction.
- Inquire about postdose adverse events before the patient leaves the investigational center.

Visit 3 (Day 28±3 days)

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

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a urine pregnancy test for women of childbearing potential.
- Review study compliance.
- Complete and review electronic headache diary.
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain a 5 mL blood sample for serum ADA assay.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the PGIC and C-SSRS Since Last Visit version questionnaires.

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

- Administer IMP.
- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.
- Evaluate for anaphylaxis or hypersensitivity reactions.
- Inquire about concomitant medication.
- Inquire about postdose adverse events before the patient leaves the investigational center.

Visit 4 (Day 56±3 days)

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

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a urine pregnancy test for women of childbearing potential.
- Review study compliance.
- Complete and review electronic headache diary.
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain an 18.5 mL blood sample and a urine sample for biomarkers analysis.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the PGIC and C-SSRS Since Last Visit version questionnaires.

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

- Administer IMP.
- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.
- Evaluate for anaphylaxis or hypersensitivity reactions.
- Inquire about concomitant medication.
- Inquire about postdose adverse events before the patient leaves the investigational center.

3. **Procedures During Administration of Investigational Medicinal Product (Open-Label Treatment Period [Visits 5 through 7, Days 84±3 through 140±3])**

Visit 5, Day 84±3 days

The following procedures and assessments will be performed predose at visit 5:

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform a full physical examination (including weight).
- Perform 12-lead ECG in triplicate.

- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform a serum β-HCG test for women of childbearing potential.
- Review study compliance.
- Complete and review electronic headache diary.
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain a 5 mL blood sample for serum ADA assay.
- Obtain an 18.5 mL blood sample and a urine sample for biomarkers analysis.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete HIT-6, SF-12, SCAT-3, PGIC, and C-SSRS Since Last Visit version questionnaires.

The following procedures and assessments will be performed at visit 5 following predose procedures and assessments:

- Administer IMP.
- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.
- Evaluate for anaphylaxis or hypersensitivity reactions.
- Inquire about concomitant medication.
- Inquire about postdose adverse events before the patient leaves the investigational center.
- Complete the Special Protocol Headache questionnaire. (to be completed at visit 5 and as the last study procedure at visit 8.)

Visit 6, Day 112±3 days

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

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain an 18.5 mL blood sample for biomarker analysis.

- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the HIT-6, SF-12, PGIC and C-SSRS Since Last Visit version questionnaires.

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

- Administer IMP.
- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.
- Evaluate for anaphylaxis or hypersensitivity reactions.
- Inquire about concomitant medication.
- Inquire about postdose adverse events before the patient leaves the investigational center.

Visit 7, Day 140±3 days

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

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain an 18.5 mL blood sample for biomarker analysis.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the HIT-6, SF-12, PGIC and C-SSRS Since Last Visit version questionnaires.

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

- Administer IMP.
- Perform injection site assessments immediately (+10 minutes) and 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. See Section 7.9 of the protocol for additional details.

- Evaluate for anaphylaxis or hypersensitivity reactions.
- Inquire about concomitant medication.
- Inquire about postdose adverse events before the patient leaves the investigational center.

Final Visit (End-of-Treatment/Early Termination/End-of-Study [Visit 8, Day 168±3 days])

The following procedures and assessments will be performed at the final visit 8:

- Perform clinical laboratory tests (serum chemistry, hematology and coagulation, and urinalysis).
- Perform 12-lead ECG in triplicate.
- Perform vital signs measurements (systolic and diastolic blood pressure, pulse, and body temperature).
- Perform beta-human chorionic gonadotropin (β-HCG) serum pregnancy test (for women of childbearing potential).
- Perform a urine pregnancy test for women of childbearing potential.
- Obtain a 4 mL blood sample for plasma concentration of IMP.
- Obtain an 18.5 mL blood sample and a urine sample for biomarkers analysis.
- Obtain a 5 mL blood sample for serum ADA assay.
- Collect a 1 mL saliva sample for biomarker analysis.
- Inquire about adverse events.
- Complete the C-SSRS Since Last Visit version questionnaire.
- Complete HIT-6, PHQ-2/PHQ-9, SF-12, SCAT-3, PGIC, and Special Protocol Headache Questionnaire.
- Inquire about concomitant medications.

4. **Unscheduled Visits**

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

Procedures performed during unscheduled visits include:

- Review electronic diary data.
- Review study compliance.

- Perform vital signs measurements (including systolic and diastolic blood pressure, pulse, and body temperature).
- Inquire about adverse events.
- Inquire about concomitant medications
- Complete the C-SSRS Since Last Visit version.

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

APPENDIX I. 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 normal (ULN) (including subjects 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[1]. In addition, the subject should be instructed to refrain from alcoholic beverages.

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

Elevation of Either ALT or AST to ≥3× ULN

Confirmation is required prior to study drug 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 study drug 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 count [CBC] 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 subject regarding symptoms.

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

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

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

Additional Tests/Evaluations:

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

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

ALT or AST ≥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:

- ALT, 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 one 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 subject will be followed according to the investigator's discretion, but a blood sample for ALT; AST; GGT; ALP; and total, direct, and 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:

- ALT, 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 study drug 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 study drug 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

- 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 J. CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

As detailed by Sampson et al 2006[2], 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 el al 2006, are as follows:

Anaphylaxis is highly likely when any 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 one of the following:
    a. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
    d. persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
    a. adult: systolic blood pressure <90 mm Hg or >30% decrease from that person's baseline

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

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[2] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-7.

APPENDIX K. CLINICAL LABORATORY TESTS

Clinical Laboratory Tests

Serum chemistry	Hematology and coagulation	Urinalysis
Calcium Phosphate Sodium Potassium Chloride Creatinine Glucose Blood urea nitrogen (BUN) Low density lipoprotein (LDL) High density lipoprotein (HDL) Triglycerides Urate Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Gamma-glutamyl transpeptidase (GGT) 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 (INR)	Color and appearance Protein Glucose Albumin Ketones Leukocyte esterase Nitrite Bilirubin Hemoglobin pH Specific gravity Microscopic tests – Bacteria – Erythrocytes – Leucocytes – Crystals – Casts

APPENDIX L. 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, polypropylene tubes (Sets A and B).

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

Shipment and Analysis of Samples

Plasma samples for all patients will be shipped from the investigational center to the central laboratory where they will be stored until shipped to the sponsor or designee for analysis. Samples will be stored in an upright position at –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 dry ice sufficient for 4 days, by next-day courier to the central 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 clinical study report 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.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

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

APPENDIX M. IMMUNOGENICITY SAMPLES

Blood Sampling and Handling

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

Label of samples should include study number, patient randomization number, nominal collection time (visit number), Set A or B, and indication that they are anti-drug antibody samples. Serum samples will be stored at a temperature of -70 ±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 dry ice sufficient for 4 days, by next-day courier to the central laboratory.

Set B samples will be sent either to the same laboratory as that for Set A on a subsequent day by next-day courier, or be retained at the investigational center until the study is completed and the clinical study report 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.

Sample shipments should be sent no later in the week than Wednesday morning for next-day delivery. Samples are not to arrive on the weekend.

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

[redacted]

APPENDIX O. 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 clinical.productcomplaints@tevapharm.com 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 of the protocol, 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 P. DATA MANAGEMENT AND RECORD KEEPING

Direct Access to Source Data and Documents

All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the 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.

The medical experts, study monitors, auditors, Independent Ethics Committee (IEC)/Institutional Review Board (IRB), and inspectors from competent authority (or their agents) will be given direct access to source data and documents (eg, medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that patient confidentiality is maintained in accordance with national and local requirements.

The investigator must maintain the original records (ie, source documents) of each patient's data at all times. The investigator must maintain a confidential patient identification list that allows the unambiguous identification of each patient.

Data Collection

Data will be collected using CRFs that are specifically designed for this study. The data collected on the CRFs will be captured in a 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, electronic patient-reported outcome tablet), these data will be sent to the investigational center, where they will be retained but not transcribed to the CRF, unless otherwise noted in the protocol. These data may also be sent electronically to the sponsor (or organization performing data management). All patient data must have supportive original source documentation in the medical records, or equivalent, before they are transcribed to the CRF. Data may not be recorded directly on the CRF and considered as source data unless the sponsor provides written instructions specifying which data are permitted to be recorded directly to the CRF.

For patients who enter a study but do not meet entry criteria, at a minimum, data for screening failure reason, demography, and adverse events from the time of informed consent will be entered in the CRF.

Data Quality Control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Oversight will be carried out as described in the sponsor's SOPs for clinical studies. Day-to-day data management tasks for this study are

delegated to a contract organization, and these functions may be carried out as described in the SOPs for clinical studies at that organization. These SOPs will be reviewed by the sponsor before the start of data management activities.

Data will be verified by the study monitor using the data source and reviewed by Data Management using both automated logical checks and manual review. Data identified as erroneous or data that are missing will be referred to the investigational center for resolution through data queries. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. Data from external sources will be compared with the information available in the CDMS, and any discrepancies will be queried.

Applicable terms will be coded according to the coding conventions for this study.

A final database lock will occur following the end-of-treatment visit (visit 8) of the last patient. At the conclusion of the study, the CDMS and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Archiving of Case Report Forms and Source Documents

Sponsor Responsibilities

The original CRFs will be archived by the sponsor. Investigational center-specific CRFs will be provided to the respective investigational centers for archiving.

Investigator Responsibilities

The investigator must maintain all written and electronic records, accounts, notes, reports, and data related to the study and any additional records required to be maintained under country, state/province, or national and local laws, including, but not limited to:

- full case histories
- signed informed consent forms
- patient identification lists
- case report forms for each patient on a per-visit basis
- data from other sources (eg, central laboratory, bioanalytical laboratory, central image center, electronic diary)
- safety reports
- financial disclosure reports/forms
- reports of receipt, use, and disposition of the 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 Q. 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.